

EEG AND CEREBRAL BLOOD FLOW IN ORGANIC DEMENTIA AND ALCOHOLISM

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Lund 1981

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Printed in Sweden
Studentlitteratur
Lund 1981

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This thesis is based upon the following publications, which in the text will be referred to by the Roman numerals.

- I G. Jóhannesson, A. Brun, L. Gustafson and D.H. Ingvar. EEG in presenile dementia related to cerebral blood flow and autopsy findings.
Acta Neurol. Scand. 56, 89-103, 1977.
- II G. Jóhannesson, B. Hagberg, L. Gustafson and D.H. Ingvar. EEG and cognitive impairment in presenile dementia
Acta Neurol. Scand. 59, 225-240, 1979.
- III B. Stigsby, G. Jóhannesson and D.H. Ingvar
Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's disease.
EEG Clin. Neurophysiol. 1981. In press.
- IV G. Jóhannesson, M. Berglund and D.H. Ingvar
EEG abnormalities in chronic alcoholism related to age.
Acta Psychiat. Scand. 1981. Accepted for publication.
- V G. Jóhannesson, M. Berglund and D.H. Ingvar
Reduction of blood flow in cerebral white matter in alcoholics related to hepatic function. A CBF and EEG study.
Acta Neurol. Scand. Accepted for publication. 1981.

ABBREVIATIONS

AD	Alzheimer's disease
Alz	Alzheimer's disease
A/P	Anterior/Posterior
%AT	Percentage activity time
BSP	Bromsulphthalein retention
CBF	Cerebral blood flow
CVD	Cerebrovascular disease
DFT	Diffuse cortical atrophy with frontotemporal accentuation (Pick)
DT	Delirium tremens
EP	Epilepsy
FC	Frontocentral mean frequency
F_{10}	Mean cerebral blood flow (f_m)
f_g	Blood flow in the cerebral gray matter (Fast component of CBF)
f_w	Blood flow in the cerebral white matter (Slow component of CBF)
$g\%$	Relative weight of gray matter (w_g)
J-C	Jacob-Creutzfeldt's disease
MF	Mean frequency
MVA	Mean voltage of analysed epoch
N	Normal EEG
P	Slightly abnormal EEG
PP	Moderately abnormal EEG
PPP	Severely abnormal EEG
rCBF	Regional cerebral blood flow

S-ALAT	Serum alanine aminotransferase
S-ASAT	Serum aspartate aminotransferase
SD	Standard deviation
TO	Temporo-occipital mean frequency

INTRODUCTION

The papers upon which this thesis is based concern the following problems: (a) The relationship of EEG to rCBF and psychometric findings in organic dementia. (b) The relationship of EEG and rCBF to age and liver function in chronic alcoholism.

The purpose of this study was to gain further information about the usefulness of EEG and rCBF in clinical diagnosis and research on cerebral disorders. Organic dementia and chronic alcoholism were chosen as objects of the study. These disorders are among the most common and most severe health problems today, not only for the individual, but also for the whole industrialized world. The increasing proportion of demented people is a well-known consequence of the changing age structure in Western society. Alcoholism, on the other hand, is an increasing social and medical problem, among other things because the use/abuse of alcohol is spreading to successively younger age groups (Hibell 1977).

It has been demonstrated that there is a correlation between EEG frequency and cerebral blood flow as well as cerebral metabolic rate of oxygen ($CMRO_2$) in dementia (Obrist et al. 1963). A regional correlation between EEG and rCBF in animals was demonstrated by Baldy-Moulinier and Ingvar (1968). In a study of the relationship between CBF and EEG, Ingvar and Sulg (1969) found a correlation between the EEG frequency and the

mean hemisphere blood flow (intra-arterial ¹³³Xenon method). The correlation was weaker in cases with regional EEG disturbances than in those with generalized EEG abnormality. Mosmans (1974) found a similar correlation, although less pronounced, using the same rCBF method and visual EEG classification. He also noted lower correlations between CBF and EEG in cases with regional abnormalities. This may be caused by regional disturbance of autoregulation with "uncoupling" of the function/flow relationship in regional disturbances, strikingly shown in acute cerebrovascular lesions (Paulson 1971, Mosmans 1974). On the other hand it has been demonstrated (Raichle et al. 1976) that the rCBF normally reflects the level of regional CMRO₂. Ingvar et al. (1976) found a significant correlation between mean EEG frequency and the cerebral oxygen uptake. Thus the available evidence supports the hypothesis that in organic dementia, EEG abnormalities and CBF reduction reflect a reduced cerebral oxygen uptake, in other words, decreased neuronal activity in the brain, most likely related to the underlying loss of neurons (Obrist 1979, Tomlinson et al. 1970).

It can therefore be assumed that the rCBF reduction as well as the EEG abnormalities recorded in organic dementia of various etiology reflect degenerative neuronal changes. Severe generalized EEG abnormality would thus correspond to diffuse degenerative (or vascular) changes, while an EEG, which is normal or only slightly abnormal, according to the criteria of conventional visual inspection, would be found in association

with less pronounced neuronal changes. In a similar way a reduction of the cerebral blood flow may be expected to mirror degenerative (sometimes secondary to vascular) neuronal changes in organic cerebral disease.

In chronic alcoholism the percentage of abnormal EEGs reported by different authors is variable, depending on the type and severity of the disease in the particular studies and also upon the varying criteria for EEG abnormality (Naitoh 1973, Begleiter and Platz 1972). In severe alcoholism, the proportion of cases with abnormal EEG is high and there are several reports that the abnormality increases with age (Greenblatt 1944, Arentsen & Sindrup 1963, Newman 1978). Interindividual, probably genetic differences in the response of EEG to alcohol have been reported (Propping 1980). Studies of the total mean cerebral blood flow (CBF) and oxygen uptake (CMRO_2) have shown normal values in patients with Korsakoff's syndrome (Hedlund et al. 1964, Simard et al. 1971). Reduced flow values were found in patients in the acute phase of Wernicke's encephalopathy (Shimojyo et al. 1967) and in acute intoxication (Battey et al. 1953). CBF and CMRO_2 values within normal limits were found in one group of abstinent problem drinkers with a mean age of 40 years, (Sutherland et al. 1960). A decreased rCBF has previously been demonstrated in the present series of alcoholics without Korsakoff's psychosis (Ingvar et al. 1969, Berglund and Ingvar 1976). Both f_g and f_w were reduced, the f_w independently of age. Reduced cerebral blood flow, f_g as well as f_w , in alcoholics as compared to

controls, was also reported by Heiss et al. (1974). Berglund and Risberg (1981), using the $^{133}\text{Xenon}$ inhalation method, found a significant reduction of rCBF during the first two days of withdrawal. The reduction was correlated to the length of the preceding drinking period, and besides, a relationship was found between auditory and visual hallucinations and elevated CBF values in the temporal, Sylvian and occipital regions.

Thus it has been shown that alcohol abuse affects the EEG as well as the rCBF. However, many aspects of these EEG and rCBF changes are still incompletely understood.

The aims of this study were:

- a) To investigate the relationship between EEG, cerebral blood flow and neuropathological diagnosis in patients with presenile dementia, especially Alzheimer's and Pick's disease, (Paper I and III).
- b) To elucidate further the relationships of EEG to psychometric findings and clinical diagnosis in presenile dementia, (Paper II).
- c) To study the relationship of EEG and rCBF to age and liver function in alcoholism (Paper IV and V).

METHODS

Regional cerebral blood flow (rCBF)

The measurement of rCBF was made by means of the intra-arterial ^{133}Xe method. This technique has been described in detail elsewhere (Ingvar and Gustafson 1970, Sveinsdottir et al. 1971, Lassen and Ingvar 1972). Eight or thirty-two detectors were used. In all cases measured with the 32-detector apparatus the values have been converted to eight regions (I: Fig. 2, V: Fig. 1). The rCBF parameters were calculated according to the height-over-area principle from the first 10 min of the clearance curve as follows: f_{10} , the mean flow, f_g , calculated from the fast component, obtained by biexponential analysis of the clearance curve, representing mainly the grey matter flow, f_w , calculated from the slow phase, representing mainly the flow in the white matter, and $g\%$, the relative weight of the grey matter calculated from the intercepts at time zero for the fast and slow components. To obtain a measure of the anterior/posterior relationship, i.e. the degree of "hyperfrontality" (Ingvar 1979, Ingvar et al. 1979), the "pre/post" ratio was calculated (III: Fig. 2) for the patients with Pick's and Alzheimer's disease. In the alcoholic series the flow values in the upper frontal (R1) and premotor (R3) regions were divided by the flow values in the posterior temporal (R7) and the occipital (R8) regions to obtain the A/P (anterior/posterior) ratio, $\frac{R1+R3}{R7+R8} = \text{A/P}$ for the four rCBF parameters f_{10} , f_g , f_w and $g\%$ (see also V: Fig. 1).

Electroencephalography

EEG recordings were done in all cases. One recording was always made in close time relation to the rCBF study. Most EEGs were recorded on a 16 channel Elema-Schönander EEG machine, some on an 8-channel Grass machine. Electrodes were placed according to the international 10-20 system (Jasper 1958). Recording was done with bipolar technique at rest in wakefulness, with closed eyes, and in most cases hyperventilation and intermittent photic stimulation was used.

Visual EEG classification. The records were classified by means of conventional visual interpretation into four classes: 1) normal, 2) slightly abnormal, 3) moderately abnormal and 4) severely abnormal (II: Fig. 1 and IV: Fig. 1). The criteria were as follows: In the normal (N) records there was symmetrical alpha activity with a normal distribution and with a mean frequency of 8-13 Hz. Slightly abnormal (P) records contained a small quantity of diffuse and/or episodic 4-7 Hz theta activity with an amplitude not exceeding 100 uV and/or a slight slowing of the background activity. Moderately abnormal (PP) records contained a larger amount of 4-7 Hz activity and/or some delta activity with diffuse distribution. Severely abnormal (PPP) records were dominated by delta and theta activity, often with episodic character. There were a few records with focal abnormalities or side differences. In these cases, the general abnormality still was the most dominant finding and, accordingly, it was used as the basis of the classi-

fication.

Manual frequency analysis was done according to the method devised by Sulg (1969 a, b), which is highly reliable, but time-consuming. Therefore the analysis was limited to the frequency bands 6-15 Hz. A 10-seconds epoch was analysed from representative samples of an anterior lead (fronto-central, FC) and a posterior lead (temporo-occipital, TO), respectively. The mean frequency was calculated for the 6-12 Hz band in each lead. There was a good correlation between the two EEG leads and a somewhat lower, but still highly significant negative correlation between the degree of EEG abnormality (visual) and the mean frequency of the EEG leads (IV: Fig. 2). Semi-automatic period-amplitude computer analysis was used in the study reported in paper III. This method of EEG analysis has been described in detail by Stigsby et al. (1973) and Stigsby (1981).

1. ORGANIC DEMENTIA

A/ Relationship between EEG and rCBF (papers I and III)

EEG was studied in all and regional cerebral blood flow (rCBF) in 14 out of 17 cases of presenile dementia (I) confirmed at autopsy (Brun & Gustafson 1976, Brun, Gustafson and Ingvar 1975, Gustafson, Brun and Ingvar 1976). There were seven cases of Alzheimer's disease and five cases with a cortical atrophy of the Pick

(DFT) type. There were also three cases diagnosed as Jacob-Creutzfeldt's disease and two with dementia of other etiology. Both the Alzheimer and the Pick patients showed fronto-temporal cortical degeneration. In addition the Alzheimer group showed severe postcentral and posterior-temporal loss of neurons. All the Alzheimer cases had from the beginning generalized EEG abnormalities which progressed slowly. In contrast, in four of the Pick (DFT) patients the first EEG was normal and in three of these remained so even late in the course when the signs of dementia were marked. A positive correlation between relative rCBF reduction in postcentral areas and an increase of EEG abnormality was found. Degenerative changes confined to frontal and anterior-temporal cortical regions with concomitant flow reduction, on the other hand, appeared to leave the alpha rhythm essentially undisturbed.

A relationship between bifrontal delta-episodes in EEG and neuropathological evidence of brain stem lesions was also found (I: Table 2).

The EEG in 9 Alzheimer cases and 4 Pick patients, all confirmed at autopsy, was studied further with semiautomatic period-amplitude analysis (III). Three EEG leads (F3-C3, T3-T5 and P3-O1) were analysed. The EEG's from 13 healthy volunteers matched for age served as controls. rCBF was measured in all the Pick patients, and in 6 of the 9 Alzheimer patients.

The Alzheimer patients showed slowing of the EEG mean frequency in all regions, with increased delta and theta, and decreased alpha and beta activity. Contrariwise, the alpha was preserved parieto-occipitally in the Pick patients. The ratio between the mean frequency of the frontocentral and the parieto-occipital regions was significantly increased in the patients with Alzheimer's disease and slightly, but not significantly decreased in the Pick patients. The Pick cases had also increased delta and theta although less so than the Alzheimer patients. The EEG in Pick's disease, which is usually considered to be relatively normal even in advanced stages of dementia, was thus also shown to be clearly different from that of healthy controls, when quantified with period amplitude analysis (III:Fig. 2 b).

In the Pick patients there was a significant correlation between regional EEG mean frequency and the flow values of the corresponding regions while this was not so in the Alzheimer patients (III:Table II). In all patients the EEG mean frequency correlated significantly with the blood flow in the white matter (f_w). The quantity of theta activity and the EEG mean voltage showed a significant negative correlation with the regional gray (f_g) and white matter (f_w) blood flow. This correlation was highest in the Pick patients. In all patients ($n=10$) the EEG "pre/post" (A/P) ratio correlated positively with the corresponding flow ratios. This was highly significant for the f_g ($p < .001$) but not for the f_w ratio (III: Table III).

B) Relationship of EEG and psychometric findings
(paper II)

EEG was related to psychometric findings in a group of 57 patients (Gustafson 1975), consisting of 19 cases of Alzheimer's disease, 7 cases of Pick's disease, 24 cases of cerebrovascular dementia (CVD) and 7 cases with dementia of other etiology (II: Table 1). The diagnoses were confirmed by autopsy in 23 out of 57 cases (Gustafson and Nilsson 1981). A significant correlation was found between psychometric groups (degree of dementia, (see Gustafson and Hagberg 1975) and EEG abnormality ($p < .001$, II: Table 3). A significant correlation between the test score and the EEG was found only for the vocabulary test and paired associates test (II: Table 4). However, on the reaction time test, colour word test and Kohs block design test, large patient groups were untestable, and a highly significant correlation was found between non-testability and severely abnormal EEG (II: Fig. 3 and Table 5). The Alzheimer and the CVD groups differed distinctly, most of the Alzheimer cases showing a severe or moderate degree of EEG abnormality and dementia, whereas in the CVD cases, the dementia was less pronounced and the EEG often normal or only slightly abnormal. A normal EEG distinguished four out of seven Pick cases from the Alzheimer cases with a comparable psychometric defect (II: Table 6).

C) Discussion

The relationship of EEG to cerebral blood flow and to psychometric findings was found to be highly different in Alzheimer's and in Pick's disease (I, II, III). In Alzheimer's disease, the cognitive impairment and the reduction of cerebral blood flow usually were accompanied by moderately or severely abnormal EEG. The patients with cerebrovascular dementia (CVD) in most cases differed from the Alzheimer cases, both the EEG and psychometric findings being generally less abnormal. It has also been demonstrated (Gustafson and Risberg 1979, Risberg 1980) that in CVD the cerebral blood flow pattern more often shows asymmetries and is more heterogeneous than in patients with Alzheimer's and Pick's disease.

The EEG abnormality according to visual evaluation showed a relationship to relative flow reduction in the posterior parts of the hemisphere (I). The quantitative EEG analysis (III) showed that the apparently normal EEG in the Pick cases contained significantly more slow activity in the anterior parts than the controls. The Pick patients had a significantly lower pre-post ratio than the Alzheimer patients in whom this ratio was significantly increased compared to normal controls. This corresponds to the blood flow reduction found in post-central regions in Alzheimer's disease and in frontal regions in Pick's disease (Risberg 1980). Regional correlations (III) between EEG mean frequency and corresponding regional flow values were significant in

the Pick patients but not in the Alzheimer's disease. There was a significant correlation between the pre/post EEG frequency (A/P EEG), and pre/post rCBF (A/P CBF) ratio in the 10 patients (III).

Thus the relationship found between EEG, rCBF and psychometric findings is different in Alzheimer's and Pick's disease. Most authors have found abnormal EEGs in almost all cases of Alzheimer's disease (Green et al. 1952, Letemendia and Pampiglione 1958, Liddell 1958, Gordon and Sim 1967). This was confirmed in the present series, all Alzheimer patients having abnormal EEG. On the other hand, as was also confirmed in the present study, the EEG in Pick's disease is often normal on visual evaluation, even in the presence of advanced dementia (Escourolle 1956, Swain 1959, Constantinidis et al. 1969). However, when studied with automatic period-amplitude analysis it turned out that the EEG in Pick's disease was also significantly different from normal controls (III).

Results of previous studies showing a correlation between the degree of EEG abnormality and the degree of dementia (Mundy-Castle 1954, Obrist et al. 1962, Weiner and Schuster 1966, Wennberg and Widén 1974) were confirmed. Patients who were untestable, most often because of aphasia, showed the most severe abnormalities, which is in accordance with the findings of Frey and Sjögren (1959).

2. ALCOHOLISM

The studies on alcoholism (IV and V) were made in order to investigate the EEG/rCBF relationship in another common form of mental disorder, different from presenile dementia, that was the subject of the studies I, II and III. These papers (IV and V) concern especially the influence of the age factor and liver function in alcoholism. For the diagnosis of chronic alcoholism to be made at least 2 of the 3 following symptoms had to be present (Kaij 1960): a) abnormal craving for alcohol after ingestion of small quantities, b) regular occurrence of blackouts following ingestion and c) physical dependence upon alcohol indicated by withdrawal symptoms when drinking has been stopped.

A) EEG and rCBF related to age (papers IV and V)

Of the fifty patients, twenty-five had an abnormal EEG (IV). The lowest proportion of abnormal EEGs (14 %) was found in the age group of 40 to 49 years. In older as well as younger patients the greater part of the records were abnormal (IV: Fig. 3). In the younger group the abnormality was in most cases mild (P), whereas six out of eight of the more abnormal (PP) records were found in patients over fifty years. In the latter group, the abnormality clearly increased with age and all five patients 60 years or over, had abnormal records. There was a statistically significant difference between the old ($\geq$ 50 years) and the

middle (40-49 years) groups ($\chi^2=6.61$, $p < .05$), and between the young (< 40 years) and the middle group ($\chi^2=7.73$, $p < .01$).

The fronto-central (FC) and temporo-occipital (TO) mean frequency of the EEG correlated negatively to age. This correlation was, however, significant only in patients 40 years or older (TO and age: $r=.42$, $p < .02$, FC and age: $r=-.40$, $p < .05$, $n=29$, IV). All cerebral blood flow (CBF) variables except f_w correlated negatively with age (V: Table 5).

There was a correlation between early onset of abuse (IV: Fig. 4 and 5) and abnormal EEG. A larger proportion of abnormal EEGs was found in the group of patients with more than 20 years duration of abuse than in the rest. The difference was not statistically significant. However, patients with moderately abnormal EEG (PP) had a significantly longer duration of abuse than the others (25 ± 11 years against 17 ± 8 years, $p < .05$).

The $g\%$ showed a significant negative correlation to duration of abuse ($p < .01$, V: Table 5). There was no significant correlation between the mean f_g or mean f_w and duration. The f_g and $g\%$, but not f_w , correlated negatively ($p < .05$) with the age at onset of abuse (V: Table 5).

B) rCBF and EEG related to liver function (paper V)

It is well known that the liver damage caused by prolonged alcohol abuse may eventually cause hepatic insufficiency with cirrhosis. The EEG changes in hepatic encephalopathy are also well known. While most alcoholics do not have overt hepatic insufficiency, laboratory tests indicating liver disturbance frequently are abnormal after a debauch (Wadstein & Skude 1979) and reduction of cerebral blood flow has been found to be most pronounced in alcoholics during the first 2 days of abstinence (Berglund & Risberg 1981). Therefore it lies close at hand to ask if liver disturbance could play a role for the EEG abnormality and rCBF reduction (Berglund & Ingvar 1976) found in the present material. This question was studied in paper V.

BSP, S-ASAT, S-ALAT and bilirubin were related to regional cerebral blood flow (V:Fig. 3). All mean hemisphere values and most regional values of the rCBF parameters correlated negatively with the liver test values. The highest correlations were between f_w and S-ASAT and were especially pronounced in the upper and posterior detector regions of the convexity, highest in the region approximately corresponding to the premotor area. The regional pattern of correlations was similar for S-ALAT, but the correlations were lower. With the exception of a single regional value (S-ASAT vs. upper frontal region (R1 in Fig. 1)) the correlations between the transaminases and f_g were not significant.

The Spearman correlations to BSP and bilirubin did not differ much between f_g and f_w . The correlation of f_g to BSP was age-dependent while the correlation of f_w to BSP was not (V: Fig. 2). The liver tests showed no significant correlation to the degree of EEG abnormality or to the frontocentral mean frequency (FC). There was a low but significant positive correlation between BSP and the temporo-occipital mean frequency (TO) which has not been further analysed. The A/P EEG ratio correlated negatively with all four liver tests, although significantly only with S-ASAT. No simple relationship was found between the EEG-variables and the cerebral blood flow.

C. Discussion

It was found that the high proportion of abnormal EEGs in the young alcoholics was related to their early onset of alcohol abuse (ONSET). Since EEG abnormality was also related to the duration of abuse (DUR), and, in patients over 40 years, to AGE, the interrelationships of these three variables are very complex. The age of onset of the abuse (ONSET) was also positively correlated to the rCBF A/P ratio (pre/post ratio, $\frac{R1+R3}{R7+R8}$, table 1) of all four rCBF variables (Jóhannesson et al. 1981, unpublished observation). For the A/P ratio of f_w (A/P_{f_w}), this correlation was significant ($r=.33$, $p<.05$). The negative correlation of A/P_{f_w} to duration was also significant ($r=-.32$, $p<.05$) and the correlation of $A/P_{f_{10}}$ to duration is still higher ($r=-.42$, $p=.003$). On

Table 1. Correlation of anterior/posterior ratios (A/P) of f_{10} , f_g , f_w and $g\%$ to age of onset of abuse (ONSET) and duration of abuse (DUR) and partial correlation of the four flow ratios to ONSET and DUR when AGE is corrected for, (Anterior/posterior ratio = $\frac{R1+R3}{R7+R8} = A/P$).

TOTAL CORRELATION

	A/P _{f10}	A/P _{fg}	A/P _{fw}	A/P _{g%}
AGE	-.21	-.06	-.03	.04
ONSET	.19	.15	.33*	.29
DUR	-.42**	-.20	-.32*	-.20

CORRECTED FOR AGE

	A/P _{f10}	A/P _{fg}	A/P _{fw}	A/P _{g%}
ONSET	.37**	.21	.41**	.32*
DUR	-.40**	-.23	-.44***	-.33*

* p < .05

* p < .01

*** p < .001

the other hand, age at examination (AGE), which was significantly correlated with ONSET and DUR, did not correlate significantly with the A/P ratio (Table 1a). This was in accordance with a previous observation showing that the relative values of the regions involved did not differ significantly between the young and the old patients (Berglund and Ingvar 1976). When AGE was partialled out, all A/P ratios except A/P f_g showed a significant positive correlation to onset and a significant negative correlation to DUR (Table 1b). These findings show that (1) early onset of alcohol abuse and (2) long duration of abuse are not only associated with a high proportion of abnormal EEGs. In addition, they significantly influence the regional flow distribution, causing a relative decrease of the cerebral blood flow in frontocentral regions (a "hypofrontal" rCBF pattern, cf. Ingvar 1979, Franzén and Ingvar 1975), especially the f_w .

The regional f_w in the alcoholics correlated better to the transaminase values on admission, than to the BSP test done on the day before or after the rCBF study (on the average about two weeks after admission). S-ASAT showed the highest correlations. This is in accordance with previous reports, the elevation of S-ASAT being regularly more pronounced in alcoholics and considered to be a more sensitive indicator of alcoholic liver disease than S-ALAT (Konttinen et al. 1970, Wadstein 1979, Sheehan & Haythorn 1979). The serum activity of ASAT decreases slowly during abstinence. Thus Wadstein & Skude (1979) found that 70 % of

alcoholic patients initially had elevated S-ASAT, and after 9 days about half of these, or 36 %, still had elevated S-ASAT values. On the other hand, it is not known if the normalization of S-ASAT is accompanied by a normalization of the f_w levels, and the present findings do not answer the question whether the f_w reduction is reversible or not.

The association between the transaminase increases at admission and the drinking pattern immediately before admission is still poorly understood. Bang et al. (1958) found a significant relationship between S-ASAT activity and blood alcohol concentration (BAC) probably indicating the severity of the abuse. However, Wadstein & Skude (1979) could not confirm this finding. A possible explanation of the present results might be that the f_w reduction is dependent on the intensity of the preceding alcohol consumption (cf. Berglund and Risberg 1981).

The age-dependent reduction of f_g (Berglund & Ingvar 1976) as well as the high proportion of abnormal EEGs in the oldest alcoholics most probably reflects the cumulative damage caused by alcohol abuse. This hypothesis is supported by pathoanatomical studies (Courville 1955), by recent computer tomography studies (Wilkinson & Carlén 1980, Bergman et al. 1980) and also by psychometric studies (Ryan 1980). The underlying mechanisms are not well understood. A possible cause is a direct effect of alcohol on the nerve cells leading to an acceleration of the normal aging (Courville 1955, Wilkinson & Carlén 1980, Ryan 1980).

The reduction of f_w in alcoholics probably has to be explained by mechanisms different from those causing the f_g decrease. While the slow component of the clearance curve probably contains fractions from blood flow in other tissues, it is generally assumed that the slow component (f_w) of the cerebral blood flow represents mainly blood flow in the cerebral white matter. Therefore it is possible that the f_w reduction reflects demyelination or some damage preceding demyelination. There is evidence of damage to the cerebral white matter/myelin in alcoholics (Lynch 1960, Lesch 1972, Wright 1979, Alling and Boström 1980). For a review of the literature on myelin changes in animal studies, see Sun (1980).

The fact that the f_w reduction was independent of age and strongly correlated to transaminase values, while the reverse was true of f_g , indicates that the fast (f_g) and slow (f_w) flow components may react differently to some hepatic factor or other toxic agents in chronic alcoholism. A discrepancy between f_g and f_w has been observed in certain other circumstances (Cervós-Navarro et al. 1971, Olesen 1974, Strandgaard 1978). The difference in the regulation of f_g and f_w is of unknown nature.

3. SUMMARY AND CONCLUSIONS

The degree of EEG abnormality is strongly correlated to the degree of cognitive impairment in organic dementia. The combination of EEG and psychometric classification distinguishes more effectively between Alzheimer's disease and cerebrovascular dementia than does psychometric classification alone. Pick's disease is often ~~cases~~ distinguishable from Alzheimer's disease by a more normal EEG of the former and different regional pattern of EEG as well as rCBF. In patients with Pick's disease the EEG, visually classified as normal, was found to differ significantly from healthy controls when analysed quantitatively with period-amplitude analysis. In Alzheimer's disease, EEG frequency and rCBF were more decreased postcentrally than in frontal regions (a "hyperfrontal" pattern) while the decrease was more pronounced frontally in patients with Pick's disease (a "hypofrontal" pattern, cf Ingvar 1979, Risberg 1980).

In alcoholism the proportion of abnormal EEGs was found to be greatest in old (≥ 50 years) and young patients (< 40 years), while it was small in the middle group (40-49 years). A correlation found between early onset of abuse and abnormal EEG explains the high proportion of abnormal EEGs in the young group while there is a correlation between EEG abnormality and age in patients over 40 years. The f_w reduction correlated strongly with elevation of S-ASAT. This correlation was independent of age. On the other hand f_g showed weak

correlations with S-ASAT and S-ALAT and its correlation with BSP was dependent on age. It is suggested that the relationship between f_w reduction and liver disturbance as reflected in the S-ASAT values may be caused by the intensity of drinking before admission. This may possibly depend on some unknown hepatic mechanism, or a direct toxic effect of alcohol.

There is some evidence of myelin damage in alcoholism, which might explain the f_w reduction. Further research is needed to settle these questions.

The results of the papers summarized here demonstrate the value of EEG and rCBF studies in presenile dementia and alcohol abuse. Admittedly, the direct use of the present results, in clinical diagnostic work, appears to be limited. However, it has been shown here that the quantitated, as well as the visually evaluated, EEG yields significant results in presenile dementia. Further research will show to what extent these findings can be used in clinical routine and in evaluation of therapeutic trials. Concerning the findings in alcoholism, the present studies showed that reduction of f_w (the slow component of the clearance curve, assumed to represent mainly blood flow in the cerebral white matter) is significantly correlated to laboratory tests indicating liver disturbance. It is suggested that the f_w reduction reflects myelin damage. The results also indicate that the probability of developing cerebral dysfunction as reflected in a high proportion of abnormal EEGs is greater in alcoholics who start their abuse at

a young age, a fact indicating higher vulnerability of the young brain to toxic effects of alcohol. Thus, alcohol abuse appears to cause a form of brain dysfunction that is fundamentally different from that caused by degeneration in presenile dementia.

Further research will be necessary to outline more in detail how the clinical psychiatric features of presenile dementia and alcohol dementia differ and how they relate to EEG and rCBF.

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ACKNOWLEDGEMENTS

The author is indebted to all staff members of the Departments of Clinical Neurophysiology and Psychiatry I, University Hospital, Lund.

My most sincere thanks are due to my tutor, professor David H. Ingvar for his constant support and valuable criticism from the beginning of this study. Dan Elmqvist, M.D., Ingmar Rosén, M.D. and Erik Ryding, M.D. are thanked for valuable advice and constructive criticism. Lars Gustafson, M.D., Bo Hagberg, Ph.D., Arne Brun, M.D. and Bent Stigsby, M.D. are thanked for pleasant and stimulating collaboration.

Ingrid Nilsson, Majvi Persson and Eva Skagert helped preparing the illustrations. Kristina Sarvik is thanked for her skillful work in typing and editing the manuscripts.

Elsevier/North-Holland Scientific Publishers, Amsterdam, and the Editors of *Acta Neurologica Scandinavica* and *Acta Psychiatrica Scandinavica* kindly gave their permission to reproduce original papers.

Reprinted from Acta Neurol. Scand. 56, 89-103, 1977.

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EEG IN PRESENILE DEMENTIA RELATED TO CEREBRAL
BLOOD FLOW AND AUTOPSY FINDINGS

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Reprinted from Acta Neurol. Scand. 56, 89-103, 1977,
with corrections.

ABSTRACT

EEG, regional cerebral blood flow (rCBF) and neuropathological autopsy data were studied in 17 patients with presenile dementia. rCBF was measured in 14 cases using the intra-arterial ^{133}Xe clearance technique. The neuropathological study included semi-serial whole brain microscopical sections in which the severity and regional distribution of the neuronal degeneration was studied, particularly in the cortex and the brain stem. There were two main diagnostic groups, seven cases of Alzheimer's disease and five cases with a cortical atrophy of the Pick (DFT) type. Both groups showed fronto-temporal cortical degeneration. In addition the Alzheimer group showed severe postcentral and posterior-temporal loss of neurons. There were also three cases with degenerative changes, suggesting Jacob-Creutzfeldt's disease. The Alzheimer cases had EEG changes which progressed slowly. In contrast, the Pick (DFT) patients had normal EEGs which could remain so even late in the course when the signs of dementia were marked. A positive correlation between rCBF reduction in postcentral areas (as evidence of neuronal loss in these regions) and an increase of EEG abnormality could be established. Degenerative changes confined to frontal and anterior-temporal cortical regions with concomitant flow reduction, on the other hand, appeared to leave the alpha rhythm essentially undisturbed. Finally, the relationship between bifrontal delta-episodes in EEG and neuropathological evidence of brain stem lesions was confirmed.

Many authors have reported a high frequency of abnormal EEGs in patients with presenile dementia. In series of patients with Alzheimer's disease neuropathologically verified, the proportion of abnormal EEGs approached 100 per cent (Green et al. 1952, Letemendia & Pampiglione 1958, Swain 1959, Gordon & Sim 1967, Nevin 1967). In most cases a diffuse irregular slowing was found and, in later stages, a complete disorganization of the EEG pattern. Focal abnormalities or side-differences were reported in some cases. Investigators basing their diagnoses on clinical grounds have also found abnormal EEGs in most cases of Alzheimer's disease (Liddell 1958, Fortin 1966), and only rarely normal records (Rosenstock 1970, Krankenhagen & Köhler 1973). Normal EEGs have, however, been found in early stages of familial cases of Alzheimer's disease diagnosed by brain biopsy (Feldman et al. 1963). Possibly, however, such genetically determined cases represent a separate clinical entity. In Pick's disease, the EEG is usually less abnormal than in Alzheimer's disease (Christian 1968). Also here, the EEG may be normal at the onset and it may remain so even in later stages of the disease (Swain 1959, Nevin 1970).

In Jacob Creutzfeldt's disease, an abnormal EEG is usually found which in many cases attains specific features with rhythmic trains of bilateral synchronous sharp-waves or high voltage polyphasic complexes. These complexes may, especially in later stages, be associated with myoclonic jerks, not always synchronously though (Jones & Nevin 1954, Nevin 1967, May 1968,

Burger et al. 1972, Elliot et al. 1974, Gaches 1974). In a small number of patients, a normal EEG has been seen even in the terminal stage (Fattovich 1960). A recent comprehensive survey of the literature on the EEG in Jacob Creutzfeldt's disease has been made by Leperre (1974).

An intellectual deterioration with early onset for which the term "multi-infarct dementia" has recently been introduced (Hachinski et al. 1974), occurs in cerebrovascular disorders. In such groups the EEG may be abnormal in about 50 per cent of the cases (Schwab 1955, Paddison & Ferris 1961). The abnormality may be diffuse or focal and side-differences may be present. Some slowing of the alpha rhythm is often found (Christian 1968). In many cases a good correlation is found between the localization of the EEG- changes and the vascular disturbance especially when this is large (Van der Drift & Magnus 1962, Niedermeyer & Uematsu 1974).

There appears to be a general assumption that the EEG abnormalities recorded in patients with presenile dementia of various etiology, mirror the degenerative (sometimes primary vascular) neuronal changes which are present in these disorders. A severe generalized EEG abnormality would thus correspond to marked diffuse degenerative (or vascular) changes, while a normal EEG would indicate less pronounced neuronal changes. Concerning the metabolic background of the EEG abnormalities in presenile dementia, Obrist et al. (1963)

found a correlation between low rCBF and slow activity EEG as well as an intellectual reduction. A reduced cerebral oxygen uptake and occurrence of dementia as well as a slow wave EEG has been found by many authors, (cf. Schmidt 1951). Ingvar & Sulg (1969) studied the relationship between CBF and EEG with the intra-arterial $^{133}\text{Xenon}$ method. In patients with diffuse EEG-abnormalities they found a correlation between the EEG frequency index and the mean hemisphere blood flow ($r=0.63$). The correlation was weaker in cases with regional EEG disturbances. Mosmans (1974) also used the $^{133}\text{Xenon}$ method and an EEG classification based on visual inspection and found a similar correlation although less pronounced. He also noted lower correlations in cases with regional abnormalities. Recently, Ingvar et al. (1976) reported a significant correlation between the mean EEG frequency and the cerebral oxygen uptake. All the studies mentioned support in principle the hypothesis that the EEG abnormalities in presenile dementia could signal a reduced cerebral oxygen uptake, as well as a reduced cerebral blood flow which, as it appears, might be grossly proportional to the severity of the EEG disturbance.

The aim of the present study has been to elucidate further the relationship between EEG, cerebral blood flow and neuropathological autopsy data in 17 patients diagnosed as suffering from presenile dementia. In all cases repeated EEG studies were made.

The present investigation is a part of a longitudinal investigation of patients with presenile dementia (Ingvar & Gustafson 1970, Gustafson & Risberg 1974, Gustafson 1975, Gustafson & Hagberg 1975, Hagberg & Ingvar 1976). In this material, a number of correlations were established between the degree and type of the intellectual deficit and the level and distribution of the cerebral blood flow. Autopsy findings also showed a remarkably good correspondence between the extent and localization of cerebral blood flow reduction and region of cortical neuronal degeneration (Brun et al. 1975, Gustafson et al. 1976).

MATERIAL AND METHODS

The investigation was performed on 17 deceased patients from a material of 57 patients in a longitudinal investigation of presenile dementia. The patients, described elsewhere (Ingvar & Gustafson 1970, Gustafson 1975), excluded cases with alcohol or drug abuse, chronic psychosis, endogenous intoxication, severe head injuries or major strokes with gross focal neurological symptoms. The age characteristics of the 17 patients are presented in Table 1.

Table 1. Age characteristics (in years) of 17 patients with presenile dementia

Sex	n	Age at onset		Age at death		Duration of the disease		Interval rCBF - death	
		mean	sd	mean	sd	mean	sd	mean	sd
F	9	56.3	± 6.6	63.9	± 7.0	7.6	± 2.4	2.6	± 1.9
M	8	51.1	± 5.1	61.4	± 5.9	10.3	± 4.8	2.9	± 1.7
Total	17	53.9	± 6.3	62.7	± 6.4	8.8	± 3.7	2.9	± 1.8

The progressive dementia of these patients had, in all but three cases (1, 2 and 16), reached a stage of severe mental deterioration at the time of death. Case 1 showed general tiredness and emotional changes, memory failure regarding recent events, slight expressive aphasia, as well as gait disturbance. Case 2 had had epileptic seizures starting one year prior to her presenile dementia, as well as amnesia, confabulation, confusion and euphoria. The clinical picture of the seven patients with Alzheimer's disease (cases 3-9) was dominated by aphasia, agnosia and apraxia. Generalized epileptic seizures were registered in four of these cases, three of which also had myoclonic twitchings. In case 3 pneumoencephalography and gammacisternography indicated hydrocephalic dementia. A Spitz-Holter ventricular shunt did not alter the clinical course of the patient. A detailed clinical and neuropathological analysis of these seven cases is given elsewhere (Brun & Gustafson 1976). The five cases with diffuse cerebral atrophy with frontotemporal accentuation showed a different symptom pattern with marked personality alterations and a progressive expressive aphasia ending in mutism. Case 10 had a Shy-Drager syndrome (Shy & Drager 1960) with postural hypotension, urinary incontinence, impotence, akinesia, and tremor. Case 13 possibly had grand mal. The symptom pattern of the three Jacob-Creutzfeldt cases was less uniform. In common, they showed severe anxiety, episodes of confusion and hallucinosis. Myoclonic twitchings were observed in case 17. Case 16 committed suicide.

EEG recordings were performed repeatedly in all cases, one recording being made in close time relation to the rCBF study. Most EEGs were recorded on a 16 channel Elema-Schönander EEG machine, some on an 8 channel Grass machine. Electrodes were placed according to the international 10-20 system. Recording was done with bipolar technique at rest in wakefulness, and in most cases hyperventilation and intermittent photic stimulation was used. The records were classified by means of conventional visual interpretation into four classes: 1) normal, 2) slightly abnormal, 3) moderately abnormal, and 4) severely abnormal. The criteria for this classification were simple: slightly abnormal records contained only a small amount of diffuse theta activity, moderately abnormal records contained more theta activity and some delta, severely abnormal records were dominated by delta and theta activity often accentuated in episodes. Apart from this general classification, focal abnormalities, side differences, the occurrence of bifrontal delta-episodes etc. were noted. Increases or decreases of the abnormalities were also registered (Figure 1).

Regional cerebral blood flow (rCBF) was measured in 14 of the 17 patients, using the intra-arterial $^{133}\text{Xenon}$ clearance technique. This method has been described in detail in a number of publications (Ingvar & Gustafson 1970, Lassen & Ingvar 1972). All flow values were referred to eight brain regions, even in cases in which 32 detectors were used. Figure 2 shows the approximate cerebral localization of the eight regions. In case 5

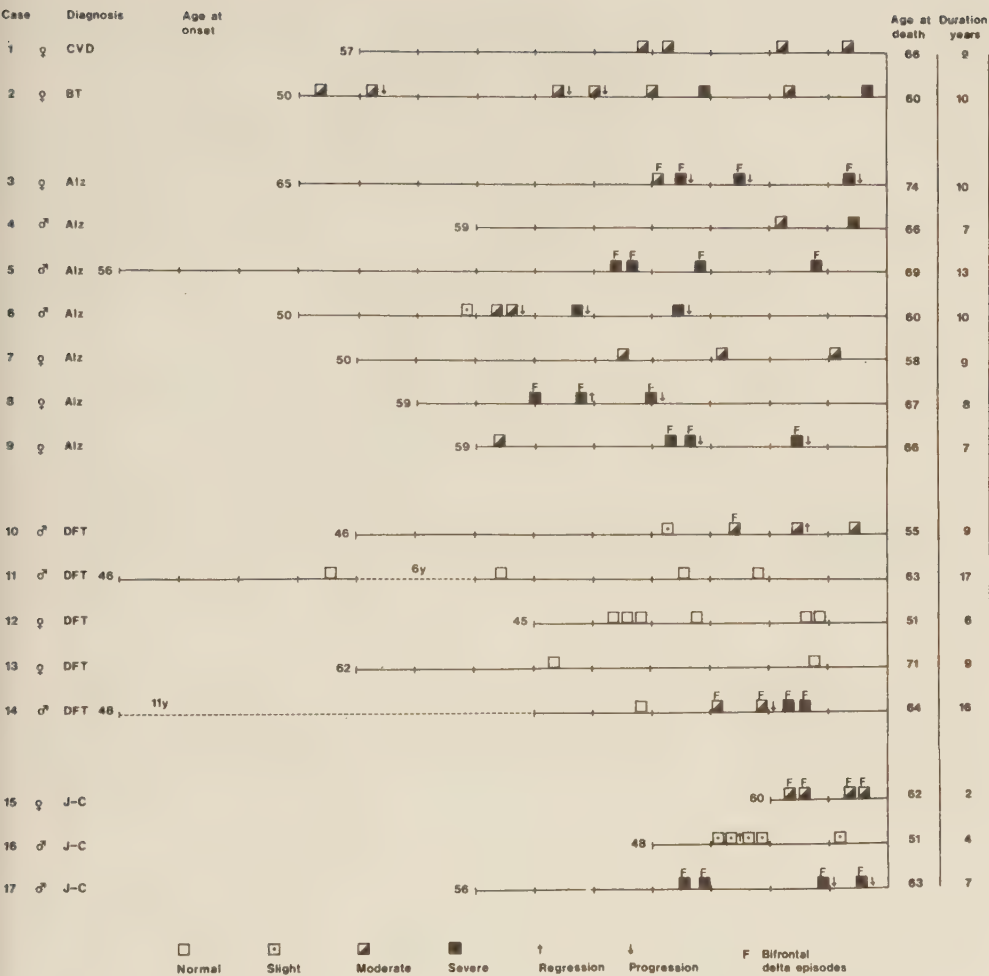


Figure 1 Degree of abnormality in repeated EEG recordings in presenile dementia. Each EEG record is represented by a square. Increase or decrease of abnormality is indicated by arrows and F indicates presence of bifrontal delta episodes. CVD=Cerebrovascular disease, BT=Bitemporal postencephalitic changes, Alz=Alzheimer's disease, DFT=Frontotemporal degeneration (Pick) J-C=Jacob Creutzfeldt's disease.

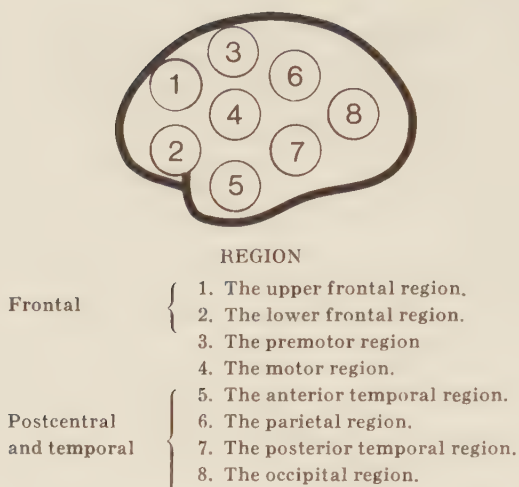


Figure 2 The approximate cerebral localization of the eight regions of rCBF measurements.

the rCBF measurements were made with only four detectors. The rCBF measurements were performed in the dominant (left) hemisphere in all but one of the 14 patients.

The neuropathological study included semi-serial whole brain microscopical sections stained with routine histological stainings, as well as silver techniques to demonstrate the histopathological features of Alzheimer's neuronopathy and argyrophilic inclusions, e.g. in Pick's disease. The whole brain sections allowed good topographic orientation and identification of various cortical fields. The severity and regional variation of the degeneration was noted, particularly within the cortex, basal ganglia and brain stem. These changes could then be correlated with the other parameters of this study.

RESULTS

Neuropathological findings

The neuropathological diagnoses are shown in Table 2 in which the severity of the brain stem lesions is also noted.

Case number 1 showed a moderate brain atrophy and rather pronounced arteriosclerosis of the basal cerebral vessels. There were, however, no large infarctions, but a diffuse mild loss of neurons, accentuated only within limited areas. The neuropathological picture appears to be best described as cerebrovascular disease (CVD).

Case number 2 had bitemporal lesions consisting of perivascular cuffs of lymphocytic cells, also seen in the thalamus. In the vicinity of these cuffs there was an astrocytic response. These changes were considered as postencephalitic.

The next group, the largest, included 7 cases of Alzheimer's disease (cases 3-9). The histopathological changes included Alzheimer's neuronopathy, the criteria of which are large amounts of senile plaques and neurofibrillar changes together with neuronal loss and gliosis. The cortical atrophy was diffuse but regionally accentuated. Thus it was consistently more severe in a lateral temporo-occipital area, as well as on the medial aspect within medial temporal limbic areas. A more detailed account of this pattern together with a presen-

Table 2. The relationship between brain stem lesion and bifrontal delta episodes.

Case no.	Diagnosis	Sex	Degenerative brain stem changes	Bifrontal episodic delta (F) in EEG
1	Cerebrovasc. d.	f	--	
2	Bitemp. postencephalit.	f	--	
3	Alzheimer's d.	f	(+)	Present in all four records.
4		m	(+)	
5		m	(+)	F present in all four records.
6		m	(+)	
7		f	(+)	F-episodes in all three records.
8		f	(+)	
9		f	(+)	F present in the last three records.
10	DFT (Pick)	m	++++	F in one record 2.5 years before death, done after two electroshock treatments.
11		m	+(+)	
12		f	--	
13		f	(+)	
14		m	(+)	F in increasing quantity in the last four records, first observed about three years before death.
15	Jacob-Creutzfeldt's d.	m	+	
16		m	--	F in all four records.
17		m	++	
				F in all four records.

tation of areas spared by the degenerative process has been presented separately (Brun & Gustafson 1976). Case 3 also had multiple recent cortical metastases of a malignant melanoma.

Cases 10-14 showed a diffuse cortical atrophy with fronto-temporal accentuation (DFT). The histopathological changes in this group in some cases suggested diagnoses of Pick's disease, but they were in general less specific, and hence a more precise diagnosis was often deemed impossible. They will be referred to as cases of DFT. The brain atrophy was rather mild in cases 10 and 11, moderate in case number 14 and pronounced in cases 12 and 13. Case number 10 showed, in addition to a cortical degeneration, a striato-nigral and olivo-ponto-cerebellar degeneration suggestive of a Shy-Drager syndrome.

Finally, three cases (15-17) showed degenerative changes indicative of Jacob-Creutzfeldt's disease with moderate cortical atrophy and degeneration of cortical neurons with shrinkage and hyperchromasia, mild cortical gliosis and a mild spongy degeneration.

Brain stem lesions (see Table 2) consisted of loss of neurons accompanied by astrocytic gliosis. In the Alzheimer group there were also scattered senile plaques and neurofibrillar tangles. Case number 10 showed the most advanced changes which, apart from neuronal loss and gliosis, consisted of partial demyelination of tracts in the pons and cerebellum.

EEG-findings

The longitudinal aspects of the serial EEG-studies are summarized in Figure 1. Each record is represented by a square corresponding to the classification in the above-mentioned four classes.

In case 1, in which the intellectual deterioration was caused by cerebrovascular disease, there was a moderate general, partly episodic EEG-abnormality which remained essentially stable for about 4 years.

Case 2 showed bitemporal degenerative changes at autopsy. The patient had epileptic seizures which started one year before the symptoms of dementia. All the EEG records were abnormal and there was an irregular tendency to an increase in abnormality.

The seven patients with Alzheimer's disease all showed abnormal records and their EEGs were the most pathological in the series. The first recordings were made 2 to 7 years before death. A progressive worsening of the abnormalities is evident in Figure 1, especially in cases 3, 4, 5 and 6. The abnormalities were of similar type (with exception of case 3) and consisting in a progressive general slowing and disorganization of the EEG pattern without distinct regional or focal changes.

In case 3 the last two records showed focal features in the left temporal regions.

In the five patients with diffuse cerebral atrophy with fronto-temporal accentuation (DFT), the least abnormal records were found. Three cases (11, 12 and 13) had normal records on all occasions. In one of these, the symptoms of dementia, personality changes and intellectual deterioration progressed during 17 years, the longest duration in the material. An EEG about 3.5 years after the onset of the disease was reported as normal and the EEG remained so, the last record was taken about 2 years before death. In case 14, in which the duration was about 16 years, the first EEG, taken about 4 years before death, was normal. In subsequent recordings a general progressive abnormality was seen. In case 10 only slight abnormality was seen in the first record about four years before death. The next record, a year later, showed a moderate abnormality. However, in the last two records (the final one taken about 6 months before death) a slight regression of the abnormality was noted.

Three cases (15, 16 and 17) showed autopsy findings consistent with Jacob-Creutzfeldt's disease. Their EEGs did not show any consistent similarities. Case 15 had a moderate episodic abnormality with some dominance on the right side, and without any definite progression between the four records. Case 16 showed a slight general and stable EEG abnormality in all records. Finally, case 17 showed a severe progressive abnormality with trains of triphasic slow waves with frontal dominance in the last record.

Bifrontal delta-episodes. In eight cases, bifrontal delta-episodes were observed in one or several of the EEG records (four Alzheimer, two DFT, and two Jacob-Creutzfeldt, Table 2). In these eight cases degenerative (non-vascular) histological changes were found in the brain stem. In the remaining nine cases, in which there were no bifrontal delta-episodes in the EEG, brain stem lesions were found only in five cases. In other words, in all cases in which bifrontal delta-episodes had been observed in the EEG, the histological investigation showed degenerative brain stem changes at autopsy. Where histological brain stem changes were absent, bifrontal delta-episodes were not observed.

Correlations between the EEG and the cerebral blood flow

The rCBF was measured in eight cerebral regions in 13 of the 17 cases. The flow values were related to the EEG record nearest in time. There was no consistent relationship between the EEG findings and the mean hemisphere blood flow parameters (Figure 3). However, the degree of EEG abnormalities tended to correlate negatively with certain regional flow values in the posterior parts of the hemisphere (Figure 3). In the occipital region, such a tendency was found for all four rCBF parameters (f_{10} , f_g , f_w , and $g\%$), but the correlations were weak. If, however, the absolute regional flow values were converted into percentual deviations from the hemisphere mean, a more distinct pattern

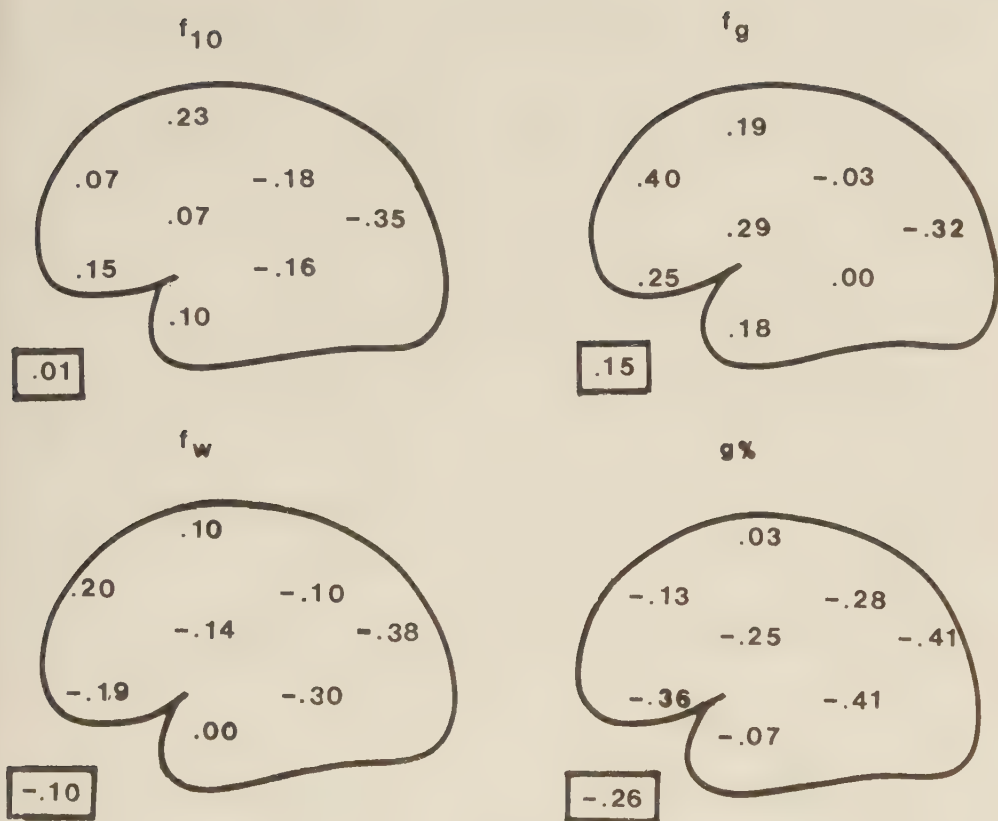


Figure 3 Product-moment correlations between the degree of EEG abnormality and rCBF in eight cerebral regions. Correlation coeff. for mean hemisphere values are given in the squares. (n=13). Sign. level: $r=.55$ $P < .05$.

was seen (Figure 4) with significant negative correlations between EEG abnormality and rCBF in the occipital regions for f_{10} ($p < .01$), f_g ($p < .001$), and f_w ($p < .05$). There were also positive correlation coefficients in precentral regions: for f_{10} in premotor ($p < .05$) and f_g in upper frontal ($p < .05$) regions. These findings imply that the more abnormal the EEG records, the lower the flow in occipito-temporal (postcentral)

regions, and the higher the flow in precentral regions.

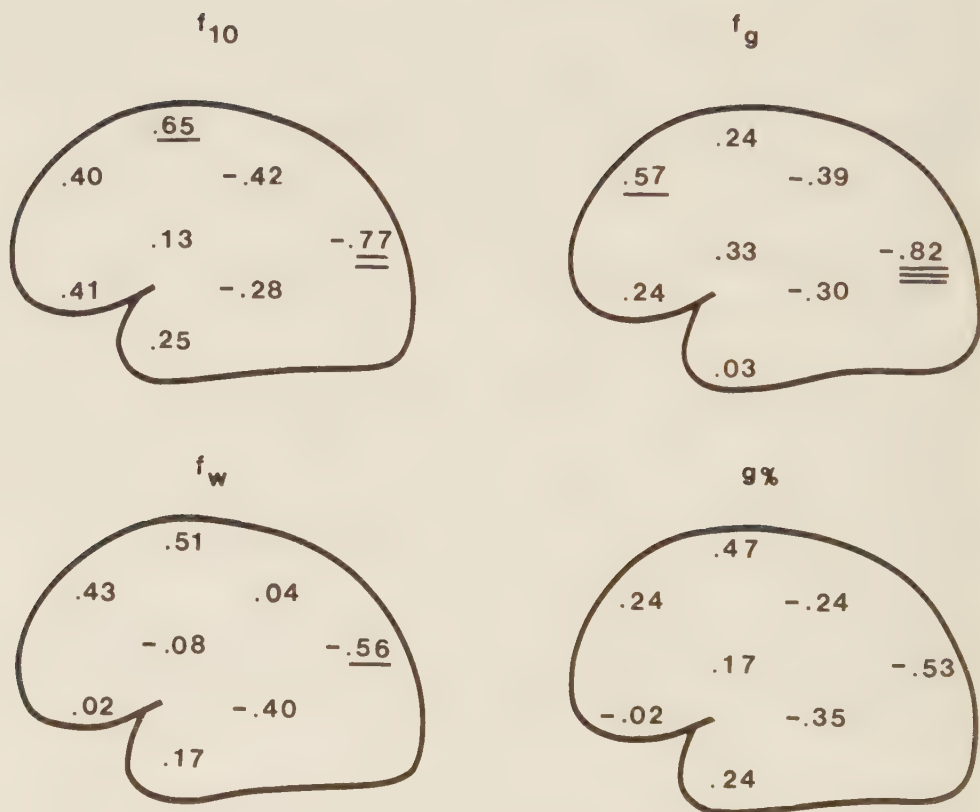


Figure 4 Product-moment correlations between the degree of EEG abnormality and rCBF (in per cent of individual hemisphere means) in eight cerebral regions. ($n=13$). Sign. levels: $r=.55$ $P < .05$, $r=.68$ $P < .01$, $r=.80$ $P < .001$.

DISCUSSION

A definite tendency can be seen in the distribution of EEG abnormalities between the two main diagnostic groups of the present patients, those with Alzheimer's disease (cases 3-9) and those with fronto-temporal accentuation of degeneration (DFT) (cases 10-14). All the Alzheimer cases had an abnormal EEG which progressed into a generalized irregular slowing. The DFT patients, on the other hand, showed normal EEGs on all occasions in three cases, in one case remaining normal for 12 years (later to deteriorate, however).

The remaining case of the DFT group (case 10) had symptoms compatible with a Shy-Drager syndrome with a severe brain stem degeneration. The first record in this case was slightly abnormal. About one year later the EEG showed a moderate general abnormality and bifrontal delta-episodes. In two later recordings, however, of which the last one was made about 5 months before death, a slight regression of the abnormality was seen.

In the three Jacob-Creutzfeldt patients (case 15, 16 and 17) no common EEG pattern was seen. In only one case were there triphasic, bilaterally synchronous waves. This confirms the reported variability of the EEG changes in this disease (May 1968) which in many ways resembles those found in diffuse cerebrovascular disorders (Nilsson et al. 1972).

Regarding the connection between bifrontal delta episodes and brain stem lesions, it should be pointed out that in most cases a considerable time interval elapsed between the final EEG recording and death (Table 1). This limits the conclusions which can be drawn from the apparent relationship between brain stem changes and bifrontal delta episodes. Moreover, it is well known that bifrontal delta episodes can be intermittent and, hence, they can be missed in a short recording. In this context it is noteworthy that patient number 10, who had a Shy-Drager syndrome, also showed the most advanced histological changes of the brain stem. This patient had bifrontal delta episodes in only one of the four EEGs taken and there were no such EEG-changes in a record taken 5 months before death.

CONCLUDING REMARKS

The most useful clinical conclusion which can be drawn from the present material is the following: In patients with intellectual deterioration with an onset in the presenium, it is often difficult to establish the etiology of the dementia. From the present longitudinal EEG study of presenile patients combined with measurements of regional cerebral blood flow and analysis of the neuropathological changes, the conclusion appears warranted that, if the EEG is highly abnormal in a case of presenile dementia, this favours the diagnosis of Alzheimer's disease. If, on the other hand, a normal or essentially normal EEG is found, it is more likely

that the patient suffers from degenerative changes mainly affecting frontal and temporal parts of the brain, a process that might represent, e.g. Pick's disease. In addition, the present series confirms the relationship between bifrontal delta episodes and the occurrence of brain stem changes. All patients in which this well-known EEG change was present showed degenerative brain stem changes, and there were no bifrontal delta-episodes in cases with a normal brain stem.

Concerning cases with presenile dementia of other etiology (cerebrovascular, postencephalitic, and Jacob-Creutzfeldt) the present material is too small to warrant any conclusions.

It then remains to be discussed why a postcentral flow reduction is coupled to a prevalence of EEG abnormalities. A tentative explanation is that a low blood flow in post-central cerebral structures signals degenerative changes not only in the hemisphere, but also in the brain stem. This would lead to an interference with subcortical centers essential for the regulation of cortical EEG-rhythms. On the other hand, degenerative changes confined to frontal and anterior temporal cortical regions might not have such general implications for structures determining the EEG rhythm. Hence, in such cases it is possible that mechanisms responsible for the regulation of e.g. the alpha rhythm may remain essentially undisturbed.

ACKNOWLEDGEMENTS

The present study was supported by the Swedish Medical Research Council (projects 14X-84, 25X-3950, 61P-4568, and 12X-2037), by the Wallenberg and the Thuring Foundations in Stockholm.

We wish to thank Miss Ulrika Serin for efficient secretarial help.

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EEG and cognitive impairment in presenile dementia

G. JOHANNESSON, B. HAGBERG, L. GUSTAFSON AND D. H. INGVAR

EEG and psychometric findings were studied in a group of 57 patients consisting of 19 cases of Alzheimer's disease, 7 cases of Pick's disease, 24 cases of cerebrovascular dementia (CVD) and a group of 7 cases with dementia of various other etiology. The diagnoses have so far been confirmed by autopsy in 23 out of 57 cases. EEG was evaluated by means of visual inspection. Psychometric studies enabled a classification into 5 psychometric defect groups according to the degree of dementia. An overall good correlation was found between the degree of dementia and EEG abnormality. A significant correlation between the test score and the EEG was found only for the vocabulary test and paired associates test. However, on the reaction time test, color word test, and Koh's block design test, large patient groups were untestable, and a highly significant correlation was found between non-testability and severely abnormal EEG. The Alzheimer and the CVD groups differed distinctly, most of the Alzheimer cases showing a severe or moderate degree of EEG abnormality and dementia, whereas in the CVD cases, the dementia was less pronounced and the EEG often normal or only slightly abnormal. Four out of seven cases of Pick's disease had a normal EEG, which distinguished them from the Alzheimer cases which had a comparable psychometric defect.

Already *Hans Berger* in 1931 reported a pathological EEG in a case of Alzheimer's disease later confirmed histologically. He also noted that there was a slowing of the EEG in senile dementia which showed a relationship to the clinical deficit (*Berger* 1932). Since then many studies on the EEG in senile intellectual deterioration and other forms of organic dementia have been published. *Hoch & Kubis* (1941) noted slow waves in some cases of organic psychosis and in some cases a parallelism between the degree of deterioration and EEG findings. In 16 cases of presenile cortical atrophy *Hill* in 1948 found 8 abnormal and 4 severely abnormal EEGs. In senile dementia *Mundy-Castle et al.* (1954) found a fall in the alpha index which was proportional to the degree of intellectual impairment. Similar findings were reported by *McAdam & Robinson* (1956) and *Frey & Sjögren* (1959). *Wennberg & Widen* (1973) found a correlation between the degree of dementia and the quantity of low frequency activity in the EEG in patients with senile dementia. *Weiner & Schuster* (1956) reported a strong correlation between the

degree of dementia and the degree of EEG slowing in patients with organic dementia of various etiologies.

In Alzheimer's disease most authors have found abnormal EEGs in almost all of the cases (*Green et al.* 1952, *Letemendia & Pampiglione* 1958, *Liddell* 1958, *Gordon & Sim* 1967, *Krankenhagen & Köhler* 1973, *Johannesson et al.* 1977). In Pick's disease a normal EEG has been reported even in the presence of advanced dementia (*Escourolle* 1956, *Swain* 1959, *Constantinidis et al.* 1969, *Nevin* 1970, *Johannesson et al.* 1977). In Huntington's chorea a low voltage EEG is often found (*Margerison & Scott* 1965, *Scott et al.* 1972). In advanced cases of Jacob-Creutzfeldt's disease the EEG often shows specific features with bilateral rhythmic polyphasic complexes (*Burger et al.* 1972, *Gaches* 1974, *Lepierre* 1974). In cerebrovascular forms of dementia ("multi-infarct dementia", *Hachinski et al.* 1974) an abnormal EEG is often found, but about half of such cases have EEG records within normal limits (*Schwab* 1955).

There are many studies of the relations between the EEG and psychometric performance, in normal persons as well as in patients. *Surwillo* (1961, 1963), reported a strong correlation between average period of the EEG and reaction time in normals. In other studies (*Boddy* 1971, *Fedio et al.* 1961), however, no such relationship was found. In retirement home residents and elderly hospitalized patients, *Obrist et al.* (1962) found that low intelligence test scores were associated with diffuse slowing of the EEG and a slow alpha rhythm, a finding consistent with those of *Burnes* (1956), *Silverman et al.* (1953) and *Thaler* (1956). In the study of *Obrist et al.* (1962) performance test results correlated better with the EEG than did verbal test results. On the other hand, in healthy aged volunteers, no significant relationships were found. *Jenkins* (1962) showed in a mixed patient group significant correlations between EEG slowing and low scores on digit symbol, block design, object assembly and performance IQ whereas verbal performance tests did not correlate with the EEG. Similarly *Liberson* (1967) found a significant correlation of EEG abnormalities with non-verbal tests, but not with vocabulary tests. Thus, there is evidence that in organic dementia the EEG carries information on the functional consequences of the degenerative cerebral changes which underlie the intellectual deterioration. In the present study this problem is further analyzed in a group of 57 patients with organic dementia in which the correlation between not only EEG and cognitive reduction was studied, but also between the EEG and the performance in specific psychometric tests.

Table 1. Age at first investigation, age at onset and duration of the disease

Sex	n	Age at first investigation			Age at onset			Duration of the disease (in years)		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
F	30	59.0 $\pm$ 5.8		43-71	54.4 $\pm$ 6.0		41-65	4.6 $\pm$ 2.2		2-10
M	27	56.1 $\pm$ 5.2		48-66	51.6 $\pm$ 5.0		40-60	4.6 $\pm$ 3.3		1-14
Total	57	57.6 $\pm$ 5.7		43-71	53.1 $\pm$ 5.7		40-65	4.6 $\pm$ 2.8		1-14

Table 2. Clinical diagnosis in 57 cases with presenile dementia

	Total	Diagnoses verified postmortem
Alzheimer's disease	19	10
Pick's disease	7	5
Cerebrovascular dementia	24	4
Mixed group		
- Jacob-Creutzfeldt's disease	3	3
- Hydrocephalic dementia	2	-
- Encephalitis	2	1
Total	57	23

MATERIAL AND METHODS

The material includes patients with various types and stages of dementia. Thus at the first investigation there were patients with early incipient, as well as advanced severe dementia. Patients with chronic psychosis, addiction, severe somatic disorders or apoplexy with gross neurological defects were excluded. The patients pertain to a longitudinal investigation of presenile dementia (Ingvar & Gustafson 1970, Gustafson & Risberg 1974, Gustafson 1975, Gustafson & Hagberg 1975, Brun *et al.* 1975, Ingvar *et al.* 1975, Hagberg & Ingvar 1976a, b, Gustafson *et al.* 1976, Brun & Gustafson 1976, Berglund *et al.* 1977, Gustafson *et al.* 1977, Johannesson *et al.* 1977, Brun *et al.* 1978, Brun & Gustafson 1978).

At the first investigation all patients went through psychiatric, neurological, psychometric and neurophysiological (rCBF and EEG) investigations. Thereafter all patients have been followed up regularly (at least once a year) and at death neuropathological investigations have been performed. The age characteristics including the duration of the disease at the first investigation are presented in Table 1.

Clinical evaluation

All cases were followed up with standardized clinical evaluations. The rating scales for the psychiatric symptoms used have been presented (and validated) previously (Gustafson & Risberg 1974, Gustafson 1975). In the present paper, the clinical material has been separated into four clinical groups (Table 2): Alzheimer's disease (AD), Pick's disease, cerebrovascular dementia (CVD) and a mixed group containing patients with

Jacob-Creutzfeldt's disease, hydrocephalic dementia or encephalitis. The diagnosis of the first three patient groups was based on a scoring schedule in which the criteria were selected from previous studies on AD (*Sjögren, Sjögren & Lindgren 1952, Brion 1966, Sjögren & Sourander 1970, Lauter 1968, 1970*), Pick's disease (*Mansvelt 1954, Escourolle 1958, Sim et al. 1966*) and CVD (*Rotschild 1956, Mayer-Gross, Slater & Roth 1969, Hachinski et al. 1974, 1975*). The clinical diagnoses were based on observations and information collected over years from the start of the investigations until 1977 or until the patient's death.

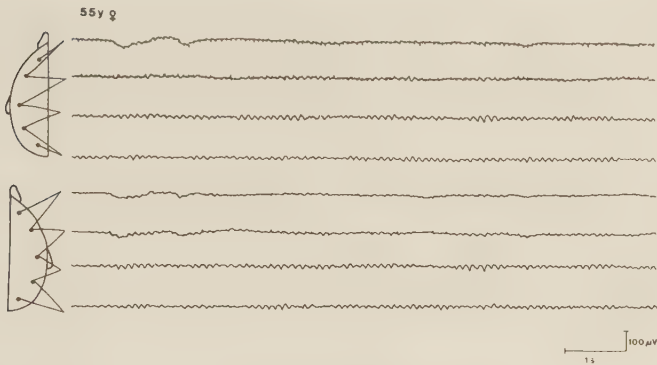
Symptoms indicating AD were slow progress of the disease with early manifestations of spatial disorientation and amnesia for remote events, apraxia, agnosia, aphasia, logorrhea and logoclonia. Other indications of AD were epileptic seizures, appearing comparatively late in the course of the disease, myoclonic twitchings, akinetic-hyper-tonic muscular tension and signs of a Klüver-Bucy syndrome. *Pick's disease* was indicated by a slow progress with early loss of insight, signs of disinhibition, irritability, confabulation, logorrhea, echolalia, mutism, amimia and signs of a Klüver-Bucy syndrome. *Cerebrovascular dementia* was diagnosed in patients with a more abrupt onset of the disease, stepwise deterioration with a fluctuating course and confusional episodes, history of arterial hypertension, stroke and early manifestations of epileptic seizures, evidence of associated arteriosclerosis and focal neurological symptoms and signs. These patients with CVD showed irritability, depression, somatic complaints and better preservation of insight and personality. An analysis of the discriminative value of the different items will be forthcoming (*Gustafson & Nilsson 1979*).

The patients were placed in the diagnostic group in which they had their highest score according to the diagnostic symptom schedule. In addition, the postmortem findings, which have been partly described elsewhere (*Gustafson et al. 1976, Brun & Gustafson 1976, 1978*) were used as a second diagnostic criterion in those patients ($n = 23$), who have died and also been investigated neuropathologically during the follow-up period. In general, there was good agreement between the clinical diagnostic groups and the postmortem neuropathological diagnosis (Table 2). When this was not the case, classification was made according to the neuropathological diagnosis. Twenty-two patients had a high AD scores and all except three cases were diagnosed as AD. In two of these, the postmortem investigation showed diffuse cerebral changes of the Jacob-Creutzfeldt type. The third case, who in addition had an extremely high Pick score, was placed in the Pick group together with six cases with high Pick scores. Twenty-eight cases showed high scores for the diagnosis of CVD. For four of these, the tentative clinical diagnoses were changed on the basis of neurological and autopsy findings. Hydrocephalic dementia was diagnosed (from air encephalography and CSF measurements) in two of these cases and one case was diagnosed as Jacob Creutzfeldt's disease postmortem. In the fourth patient with high CVD as well as high Pick scores, the autopsy showed bitemporal encephalitis. The second case with the diagnosis of encephalitis, which was based on the neurological and CSF findings had relatively low AD, Pick and CVD scores.

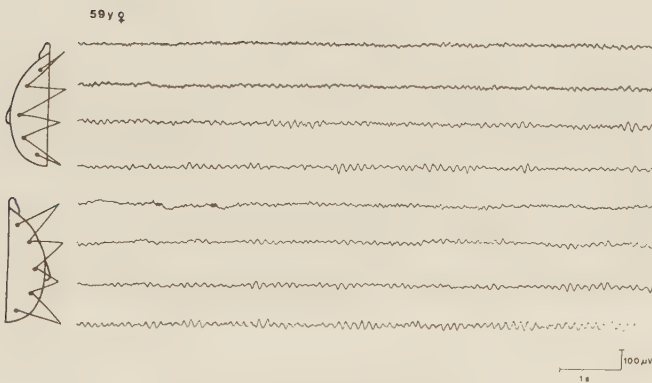
EEG methods

Repeated EEG recordings were made in all 57 cases. For the present study that record was used which was taken in immediate connection with the first psychometric examination. Almost all EEGs were recorded on a 16-channel Siemens Elema EFG machine, a small number on an 8-channel Grass machine, both used with a lower frequency limit of 0.3 and a higher at 70 Hz. The electrodes were placed according to the international 10-20 system (*Jasper 1958*) and bipolar recording was made at rest in wakefulness

Figure 1a. Sample of EEGs from the four different EEG classes.



A: Normal EEG (N).

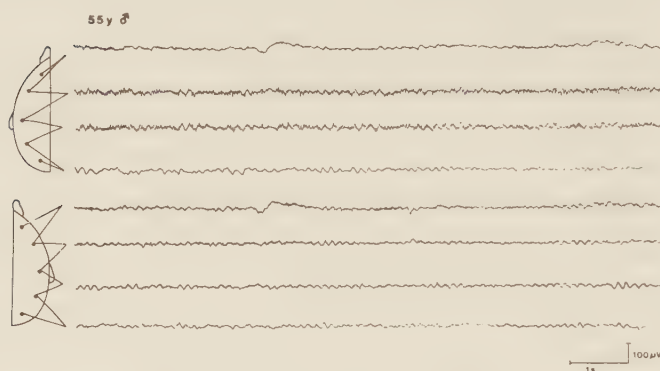


B: Slightly abnormal EEG (P)

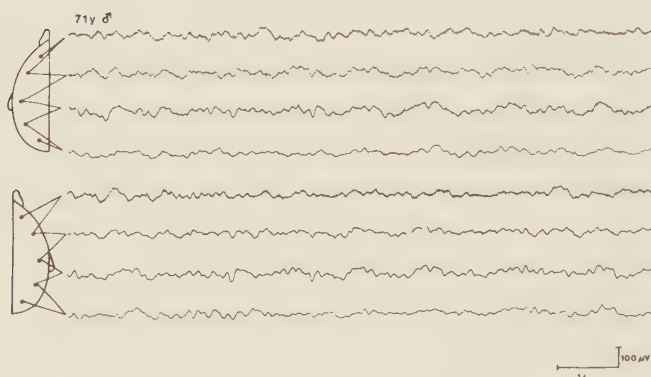
with closed eyes. The records were classified by means of conventional visual inspection into four classes: 1/ normal (N), 2/ slightly abnormal (P), 3/ moderately abnormal (PP), 4/ severely abnormal (PPP) (Figure 1). The criteria were as follows: in the *normal* (N) records there was symmetrical alpha activity, with normal occipito-parieto-temporal distribution and with a mean frequency above 8 Hz. *Slightly abnormal* (P) records contained a small quantity of diffuse or episodic 4–7 Hz theta activity with an amplitude not exceeding 100 μ V. *Moderately abnormal* (PP) records contained a larger amount of 4–7 Hz activity of higher voltage and/or some 0.3–3 Hz delta activity with diffuse distribution. *Severely abnormal* (PPP) records were dominated by delta and theta activity, often with episodic character.

There were in the material very few records with focal abnormalities or side differences. In these cases the general abnormality was still the most dominant finding. Accordingly, it was used as the basis of classification. All records were classified by

Figure 1b. Sample of EEGs from the four different EEG classes.



C: Moderately abnormal EEG (P)



D: Severely abnormal EEG (PPP)

the same physician who knew neither the psychometric results, nor, in most cases, the diagnoses.

Psychometric methods

Cognitive functions were measured with a battery of conventional psychometric tests as described by Hagberg & Ingvar 1976. The following tests were used in the present analysis:

- Vocabulary of the Wechsler-scale-type to measure verbal ability (Wechsler 1958)
- Block design, a spatio-perceptual performance test also from the Wechsler scale to measure inductive reasoning and form perception (Wechsler 1958)
- Paired associates as a measure of immediate verbal memory (Cronholm & Molander 1954)
- Color Word Test as a measure of intellectual speed and concentration (Stroop 1935, Smith & Nynan 1959)

e) Visual reaction time test, simple and choice.

The test results were evaluated against the performance in a matched control group (Hagberg & Ingvar 1976).

The following classification established in an earlier analysis (Hagberg & Ingvar 1976) was also used here for an overall judgment of degree and type of cognitive reduction.

C1 No differences from the control group in the performance of any test

C2 Significant differences only with regard to short-term memory, verbal as well as spatial

C3 General intellectual reduction with retained verbal functions

C4 General and verbal reduction with anomia, acalculia and disturbed spatial ability

C5 General intellectual reduction with signs of aphasia, agnosia, apraxia and loss of spatial ability.

These groups represent successive stages of increasing intellectual reduction in progressive organic dementia.

RESULTS

Figure 2 shows the main result, the relationship between the degree of EEG abnormality (EEG classes, N, P, PP, and PPP) and the degree of dementia (the five psychometric defect groups C1–C5). It is seen that the more abnormal the EEG was, the more pronounced was the intellectual reduction. In fact, all except one of the cases belonging to the most defective group C5 had severely or moderately pathological EEGs while all except two of the cases in group C2 had normal or only slightly pathological EEGs. Groups C3 and C4 had an intermediate position. In Table 3 the same results are

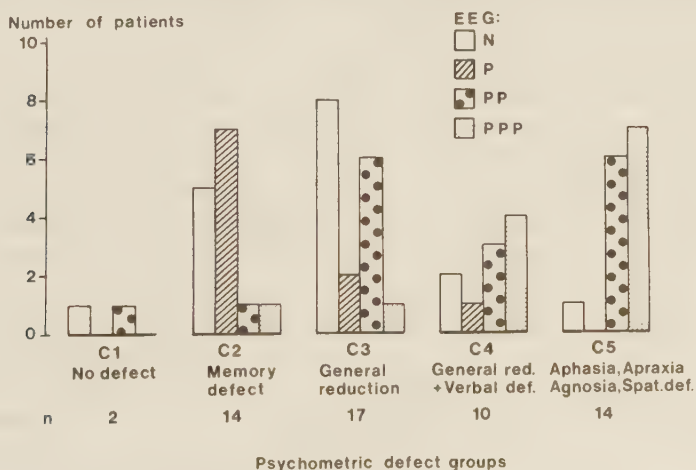


Figure 2. Psychometric defect groups related to EEG. For explanation see text.

Table 3. Correlation between EEG-classes and psychometric defect groups

	C1 + C2 + C3	C4 + C5	n
PP + PPP	10	20	30
N + P	23	4	27
n	33	24	57

$\Phi = 0.52$ N = Normal EEG PP = Moderately pathological EEG
 $P < 00.1$ P = Slightly pathological EEG PPP = Severely pathological EEG

shown in a fourfold point table, in which the significant correlations are seen.

In Table 4 a comparison is made between EEG class and score in six different psychometric tests. Only testable patients are included, and, hence, the groups are unequal in size. The difference in psychometric performance between testable patients with normal or slightly pathological EEG, and those with moderately or severely abnormal EEG was statistically significant for the vocabulary test and the paired associates test.

In Figure 3 and Table 5, the patients are divided into those who were testable (T) and untestable (U). Although the results in separate test differed somewhat quantitatively, the tendency was similar in all five. The untestable patients had in general severely or moderately abnormal EEGs whereas the majority of the testable patients had normal or slightly pathological EEGs. This dichotomy is best illustrated by the results in the Koh's block design test where only one of the untestable patients had a normal EEG, the rest all having a severely or moderately pathological EEG. On the other hand, only one of the testable cases had a severely pathological EEG. The correlations are statistically significant (Table 5).

In Table 6, the distribution of the combined EEG and psychometric findings is shown for the four diagnostic groups. Alzheimer's disease, Pick's disease, and cerebrovascular dementia. The fourth group was heterogeneous (mixed group, Table 2). The four groups showed a definite pattern as to EEG and psychometric defect groups. In Alzheimer's disease the patients were found in the lower right corner of the matrix whereas the cerebrovascular cases were in the diagonally opposite corner with their more normal EEG and less pronounced intellectual defects. Cases diagnosed as Pick's disease had a varying degree of dementia (from C2 to C5) whereas the EEG in four cases out of seven was normal and apparently did not correlate with the degree of dementia (Johannesson *et al.* 1977). The mixed diagnostic group, as expected, did not show any distinct distribution pattern with respect to the degree of dementia and EEG abnormality.

Table 4. Test results in six different tests related to EEG findings.
Comparison between the mean psychometric scores and the EEG abnormality.
For further explanation see text.

EEG	Reaction time simple n = 38	Reaction time choice n = 33	Colour-word test n = 29	Koh's block design n = 34	Vocabulary test n = 56	Paired associates n = 44
N + P	n = 24 $\bar{x}$ = 60.57 SD = 28.60	n = 24 $\bar{x}$ = 75.33 SD = 39.83	n = 22 $\bar{x}$ = 219.23 SD = 85.18	n = 25 $\bar{x}$ = 15.52 SD = 6.62	n = 26 $\bar{x}$ = 24.62 SD = 16.42	n = 25 $\bar{x}$ = 11.64 SD = 6.54
PP + PPP	n = 14 $\bar{x}$ = 68.74 SD = 20.01	n = 9 $\bar{x}$ = 71.44 SD = 12.64	n = 7 $\bar{x}$ = 269.29 SD = 227.77	n = 9 $\bar{x}$ = 12.56 SD = 8.49	n = 30 $\bar{x}$ = 14.20 SD = 14.50	n = 19 $\bar{x}$ = 6.16 SD = 7.17
P (N+P/ PP + PPP)	N.S.	N.S.	N.S.	N.S.	t = 2.52 P < .01 (one-tailed test)	t = 2.64 P < .01

EEG related to testability on five different psychometric tests.

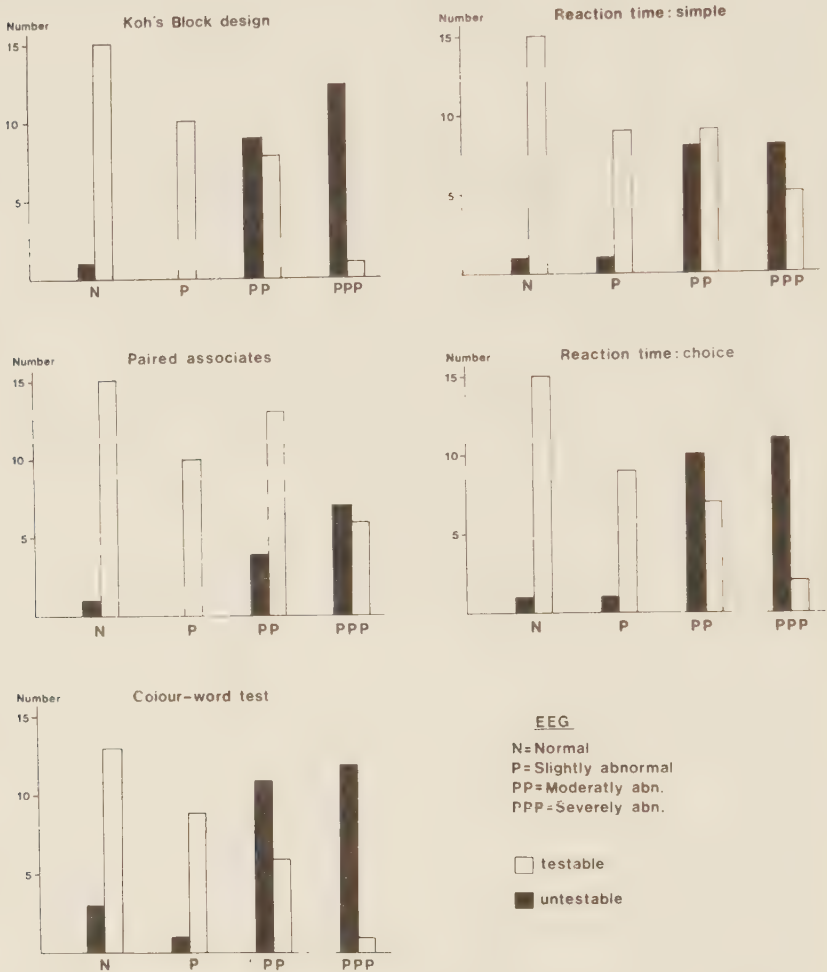


Figure 3. Patient material divided according to testability in each of the different psychometric tests. The relation between the score of the testable patients (white columns) and the EEG is further analyzed in Table 4. For statistical analysis of the difference between the testable (T) and the untestable (U), see Table 5.

Table 5. Fourfold point correlations between testability on five different tests and EEG abnormality

EEG	Reaction time simple		Reaction time choice		Color word test		Koh's block design		Paired associates	
	T	U	T	U	T	U	T	U	T	U
N + P	24	2	24	2	22	7	25	1	25	1
PP + PPP	14	16	9	21	4	23	9	21	19	11
	$\Phi = 0.487$ $P < 0.001$		$\Phi = 0.632$ $P < 0.001$		$\Phi = 0.62$ $P < 0.001$		$\Phi = 0.676$ $P < 0.001$		$\Phi = 0.4$ $P < .01$	

T = Testable

U = Untestable

Table 6. EEG-classes and psychometric defect groups in four diagnostic groups.

Alzheimer's disease n = 19						Pick's disease n = 7					
N						N			1	2	1
P				1		P					
PP			1	3	4	PP		1			1
PPP			1	2	7	PPP				1	
	C1	2	3	4	5		C1	2	3	4	5
Cerebrovascular disease n = 24						Mixed group n = 7					
N	1	4	9			N					
P			5	1		P		1	1		
PP	1			3		PP			2		1
PPP						PPP		1		1	
	C1	2	3	4	5		C1	2	3	4	5

DISCUSSION

This study is limited by the small number in each of the psychometric groups and the diagnostic groups, respectively. The EEG classification was made with respect to EEG abnormality treated as a single variable. A more detailed evaluation by means of computer analysis is under way.

The present findings confirm an overall good correlation between the degree of intellectual defect in organic dementia and EEG abnormality. The correlations of the EEG to different psychometric tests, however, showed considerable variations.

The groups upon which the correlations are calculated differ considerably in size. There is thus a much larger proportion of patients with severe dementia included in the vocabulary and paired associates test. This may partly explain why the correlations reach a significant level in these tests only (Table 5). The absence of significant correlations between test values and EEG in the reaction time test, the color word test and Koh's block design test, is explained by the fact that large groups representing untestable patients have been excluded. Those are the cases with the most pronounced intellectual reduction. When a patient is untestable this is most often due to aphasia which makes the instruction and/or the responses uncomprehensible. The division of the case material into two categories, testable (T) and untestable (U) (Figure 3 and Table 5), represents a further analysis of the total patient material with regard to this dichotomy. In the "U" category pronounced EEG abnormalities were significantly more frequent. It can thus be concluded that patients with signs of aphasia showed the most severe EEG abnormalities, a finding in agreement with those of *Frey & Sjögren* (1959).

The results in the comparison between diagnoses, psychometric defect groups and the EEG (Table 6) show that, in general, there was a correspondence between the degree of EEG abnormality and dementia. Concerning the diagnostic groups, it must be pointed out that the differentiation is based on information collected over years, while EEG and psychometric testing refer to the first investigation of the patient. When the patient material was divided according to diagnosis, a continuum as to the degree of dementia appeared. At one end of this continuum there was a cluster of Alzheimer cases, with severe dementia and in most cases a severely or moderately pathological EEG. Patients with cerebrovascular dementia were found at the other end with less severe psychometric defect and EEG changes. In the Pick group, and in the heterogeneous fourth group, the degree of psychometric defect and EEG appeared unrelated. The proportion of normal EEGs in the Pick group sharply distinguished these patients from the Alzheimer cases in whom the psychometric defect often was of similar severity. This difference between the EEG in Alzheimer's disease and Pick's disease has been dis-

cussed in a previous paper (Johannesson *et al.* 1977). In the heterogeneous fourth group the number of patients in each diagnostic category is too small for any conclusions to be drawn.

Previous studies by several authors showing a correlation between the degree of dementia and the degree of EEG abnormality (Berger 1932, Mundy-Castle *et al.* 1954, Weiner & Schuster 1966, Wennberg & Widén 1973) are thus confirmed by the present study.

The frequent finding of a normal EEG in Pick's disease still remains unexplained. In this disease, the neuropathological changes are mostly confined to anterior cortical regions. As proposed (Johannesson *et al.* 1977), it appears that in Pick's disease subcortical pacemakers regulating the electrical activity of the brain are left relatively unaffected and thus continue to function normally or nearly so, even in the presence of severe cortical involvement and advanced dementia.

Further, the criteria of "normality" may be questioned, since conventional visual inspection uses only a limited part of the information contained in the EEG. By the use of automatic analysis the presence of EEG abnormalities in Pick's disease may possibly be disclosed.

ACKNOWLEDGMENTS

The present study was supported by the Swedish Medical Research Council (project numbers B78-14X-84-14C, 21P-5144 and 25X-03950), and by the Wallenberg and Thuring Foundation in Stockholm.

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Received December 12,
accepted December 19, 1978

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REGIONAL EEG ANALYSIS AND REGIONAL CEREBRAL BLOOD
FLOW IN ALZHEIMER'S AND PICK'S DISEASE

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The EEG abnormalities in Alzheimer's disease are well known. They usually begin with a progressive general slowing of the background activity and an increased admixture of delta and theta waves (Letemendia and Pampiglione 1958, Gordon and Sim 1967, Waldton, thesis 1973). However, normal EEG's have been reported in some familial cases confirmed by brain biopsy or autopsy (Feldman et al. 1963), as well as in a few non-verified cases (Rosenstock 1970, Krankenhagen and Köhler 1973). In contrast, the EEG in Pick's disease has often been found to be normal or nearly normal, even in advanced stages of dementia (Swain 1959, Nevin 1967).

The cerebral blood flow and the cerebral oxygen uptake are decreased in both Alzheimer's and Pick's disease (Ingvar and Gustafson 1970, Obrist et al. 1970, Simard et al. 1971, Gustafson and Risberg 1979, Risberg 1980). However, in early stages of Alzheimer's disease a normal cerebral blood flow has been reported (O'Brien and Mallett 1970, Hachinski et al. 1975).

The reduction of cerebral blood flow correlates with the degree of mental deterioration (Ingvar and Gustafson 1970, Obrist et al. 1970, Gustafson and Risberg 1974, Hagberg and Ingvar 1976). Similarly, a significant correlation between the EEG abnormality and the severity of cognitive reduction in Alzheimer's disease has been reported (Jóhannesson et al. 1979), but no association was found between EEG abnormality and duration

of the illness (Gordon and Sim 1967). However, in some rather early cases of Alzheimer's disease, Gordon (1968) found a progressive EEG deterioration during an observation period of one to four years. A slow EEG deterioration during the course of the disease was also noted by Jóhannesson et al. (1977).

In the present study, the EEG in neuropathologically verified cases of Alzheimer's and Pick's disease was analysed quantitatively and related to the regional cerebral blood flow (rCBF) measured with intra-arterial ^{133}Xe clearance technique. An age-matched group of healthy volunteers served as control for the EEG analysis. All studies were carried out at rest, i.e. with the patients awake and conscious, but as far as possible undisturbed by sensory stimulation.

MATERIAL AND METHODS

Four patients with Pick's disease (2 females and 2 males) were examined at a median age of 57 years (range 49-66 years) and nine patients with Alzheimer's disease (6 females and 3 males) at a median age of 61 years (range 53-70 years). The mean age at death was 60 years (range 51-71) for the Pick patients, and 65 years (range 58-74) for the Alzheimer patients. Thus the interval between examination and death was about the same for the two groups (3.5 years (range 2-5 years) for the Pick patients and 3.8 years (range 2-7 years) for the Alzheimer patients). The duration of disease ranged from 8-12 years. At the time of the rCBF and EEG examination all patients showed severe intellectual deterioration with memory disturbances and marked reduction of cognitive abilities. The intellectual reduction was less pronounced in the Pick patients than in the Alzheimer patients, despite approximately the same duration of the illness. However, the Pick patients showed more emotional and personality alterations.

The diagnoses were confirmed by autopsy, which included semi-serial whole brain microscopic sections used for silver staining. A detailed clinical and neuropathological analysis of the patients has been given elsewhere (Brun and Gustafson 1976).

Thirteen healthy volunteers (7 females and 6 males, median age 59 years, range 45-71 years) served as controls for the EEG analysis.

Regional cerebral blood flow was measured in the four Pick patients, and in six of the nine Alzheimer patients, by the intra-arterial ^{133}Xe clearance technique, which in most cases was performed in conjunction with carotid angiography, using 8 or 32 detectors. During the rCBF measurements strict resting conditions were observed with silence in the laboratory. The patients had a small pad covering their eyes. The following flow parameters were calculated from the clearance curves: 1) mean cerebral blood flow (f_m), 2) grey matter blood flow (f_g), 3) white matter blood flow (f_w), and 4) the relative weight of the grey matter (w_g) (Lassen and Ingvar 1972). The results of the flow measurements related to the clinical findings have already been described (Ingvar and Gustafson 1970, Gustafson and Risberg 1974, Gustafson 1975, Gustafson and Hagberg 1975, Hagberg and Ingvar 1976, Ingvar et al. 1978), as have their relations to the distribution of cortical degenerative changes (Gustafson et al. 1977, Jóhannesson et al. 1977). The rCBF was measured in the left hemisphere, and all flow values were referred to eight brain regions even in cases where 32 detectors were used (Fig. 1). Pre/postcentral flow ratios ("pre/-post" ratio) were obtained by dividing the mean flow parameters of the precentral regions in Fig. 1 by the mean parameters of the postcentral regions.

Measurements of total mean cerebral oxygen uptake based upon mean hemisphere regional blood flow and arteriovenous difference were not carried out (Franzén and Ingvar 1975).

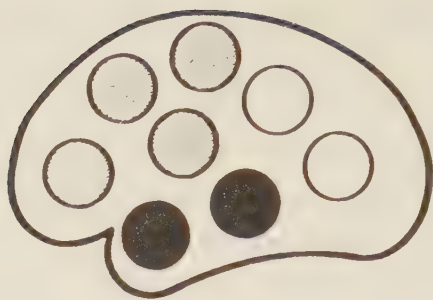


Figure 1. The approximate cerebral localization of the eight regions of the rCBF measurements. The mean flow values of the grey regions were related to the EEG parameters of the F3-C3 derivation, the black regions to T3-T5, and the white regions to P3-O1. The ratio between mean flow parameters obtained from the grey and the white regions constituted the "pre/post" flow ratio.

A resting EEG with eyes closed was recorded not more than two days before, or after, the rCBF measurements, using bipolar montages on an 8 or 16 channel EEG machine (band pass 0.5 to 70 Hz). The scalp electrodes were placed according to the international ten-twenty electrode system (Jasper 1958). Twenty seconds of artefact free representative resting EEG from the F3-C3, T3-T5 and P3-O1 derivations of the EEG paper trace were digitized by means of a semi-automatic curve follower (D-MAC pencil follower) connected to a general purpose digital computer (IBM 1800) for later period-amplitude analysis. The analysis epoch of 20 seconds was chosen in accordance with Sulg (1969). By zero-

crossing and peak detection the period and amplitude of each single EEG wave were measured. The percentage activity time (%AT) and the mean peak-to-peak voltage (MV) were calculated for each of 21 frequency bands, covering the range from 0.5 to 28.6 Hz. The EEG mean frequency (MF) and the EEG mean voltage of the analysis epoch (MVA) were then calculated. This method of EEG analysis has been described in detail by Stigsby et al. (1973), and the curve follower, its connection to the computer and the computer programs used for the digitizing have also been described (Stigsby and Rasmussen 1970). The variation due to the semi-automatic digitizing expressed as the standard deviations of the differences between double determinations of MF and MVA was 0.3 Hz and 0.8 uV, respectively (Stigsby, unpublished work). To obtain a measure of the pre/postcentral relationship, i.e. the degree of "hyperfrontality" (Ingvar 1979) the ratios between EEG parameters from F3-C3 and P3-O1 ("pre/post" ratio = $EEG_{F3-C3} \div EEG_{P3-O1}$) were calculated.

The results of the EEG analysis in the Alzheimer and the Pick patients were compared with the results from the control group using the MannWhitney U-test. This was done for the %AT and MV frequency distributions as well as for the MF and the MVA. The relation between EEG and rCBF parameters was tested by the Spearman Rank Correlation Coefficient (Siegel 1956).

RESULTS

Alzheimer patients

The Alzheimer patients showed a slowing of the EEG mean frequency and a decrease of the mean voltage (Table I). The activity within the delta and theta frequency bands was increased, and decreased within the alpha and beta frequency band. The mean voltage of the delta activity was increased, whereas the mean voltage of the alpha activity was decreased as compared to the controls (Fig. 2a). When visually evaluated, all these EEG's were considered as moderately to severely abnormal, with a diffuse slowing and deterioration of the background activity. Additionally short trains of bifrontal delta waves of increased amplitude (100-250 μ V) were noted in some records.

The mean "pre/post" frequency ratio was 1.30 (S.D.=0.33, which implies a significant increase ($p < 0.05$) compared to the controls (1.09, S.D.=0.21).

Pick patients

In the four Pick patients the EEG mean frequency was also decreased, although less so than in the Alzheimer patients (Table I). The amount of slow activity especially within the delta and theta range was increased, but the alpha activity was well preserved especially in the parieto-occipital region. The mean voltage of the delta activity was increased, whereas the mean voltage of

Table 1. The EEG mean frequencies (MF (mean $\pm$ SEM) in Hz) and mean voltages (MVA (mean $\pm$ SEM) in μ V) in the fronto-central, temporal and parieto-occipital regions of the left hemisphere of 9 Alzheimer patients, 4 Pick patients and 13 healthy control subjects. Significant differences between the groups are indicated by the obtained level of statistical probability (Mann-Whitney U-test).

EEG parameters	Controls N = 13 $\bar{x} \pm$ SEM	Difference Pick - controls	Pick N = 4 $\bar{x} \pm$ SEM	Difference Pick - Alzheimer	Alzheimer N = 9 $\bar{x} \pm$ SEM	Difference Alzheimer - controls
MF (F3-C3)	11.3 $\pm$ 0.60	p < 0.02	7.1 $\pm$ 0.24	n.s.	6.7 $\pm$ 0.74	p < 0.002
MF (T3-T5)	11.1 $\pm$ 0.25	p < 0.002	6.9 $\pm$ 0.40	n.s.	6.7 $\pm$ 0.62	p < 0.002
MF (P3-O1)	10.5 $\pm$ 0.27	p < 0.002	7.6 $\pm$ 0.63	p < 0.05	5.2 $\pm$ 0.43	p < 0.002
MVA (F3-C3)	14 $\pm$ 1.2	n.s.	9 $\pm$ 1.1	n.s.	11 $\pm$ 1.2	n.s.
MVA (T3-T5)	17 $\pm$ 1.2	n.s.	12 $\pm$ 2.8	n.s.	12 $\pm$ 0.8	p < 0.02
MVA (P3-O1)	16 $\pm$ 1.1	n.s.	12 $\pm$ 1.6	n.s.	10 $\pm$ 0.8	p < 0.002

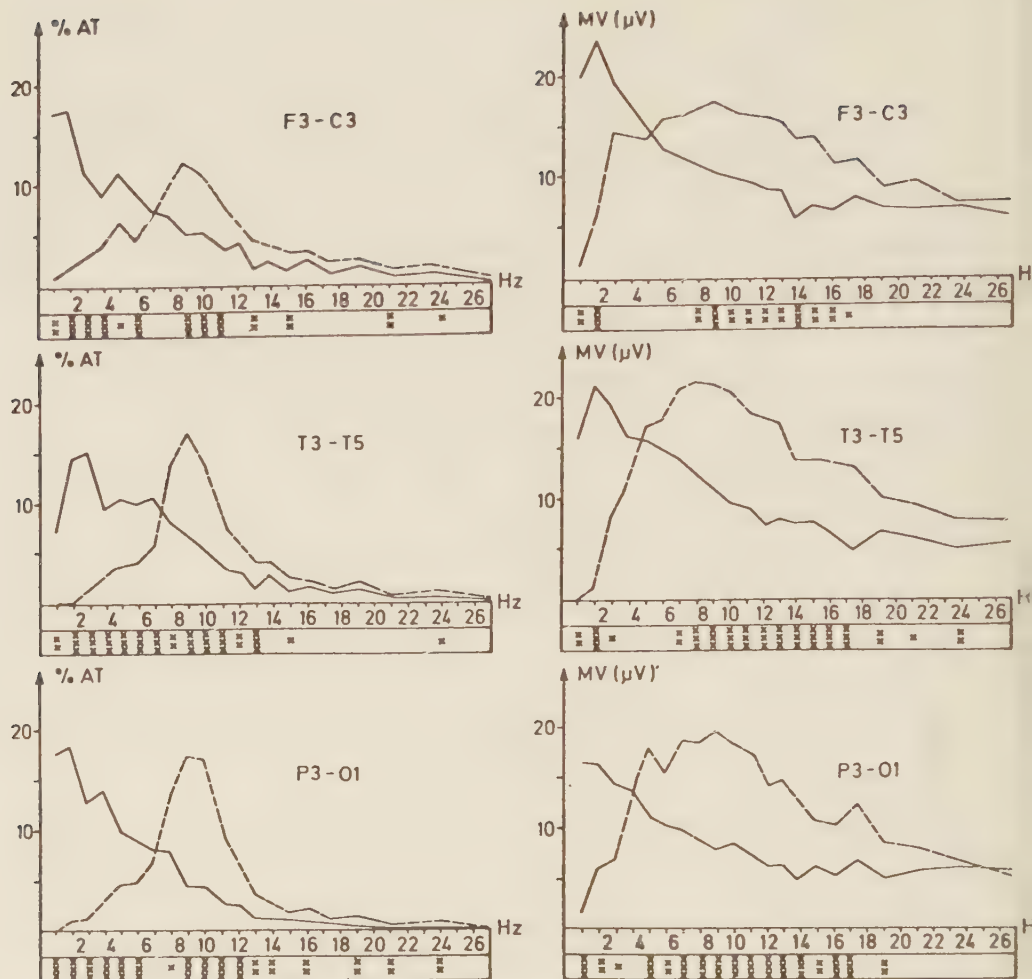


Fig. 2 a

Figure 2 a-b. The mean activity distributions (left column) and the mean voltage distributions (right column) in EEG's from the frontocentral, temporal and parieto-occipital region of the left hemisphere in 9 patients with Alzheimer's disease (solid curves) (a), in 4 patients with Pick's disease (solid curves) (b) and in 13 healthy control subjects (stippled curves). Significant differences between the patients and the controls are indicated by asterisks at the corresponding frequency bands (x: $p < 0.05$, xx: $p < 0.025$, xxx: $p < 0.002$, Mann-Whitney U-test).

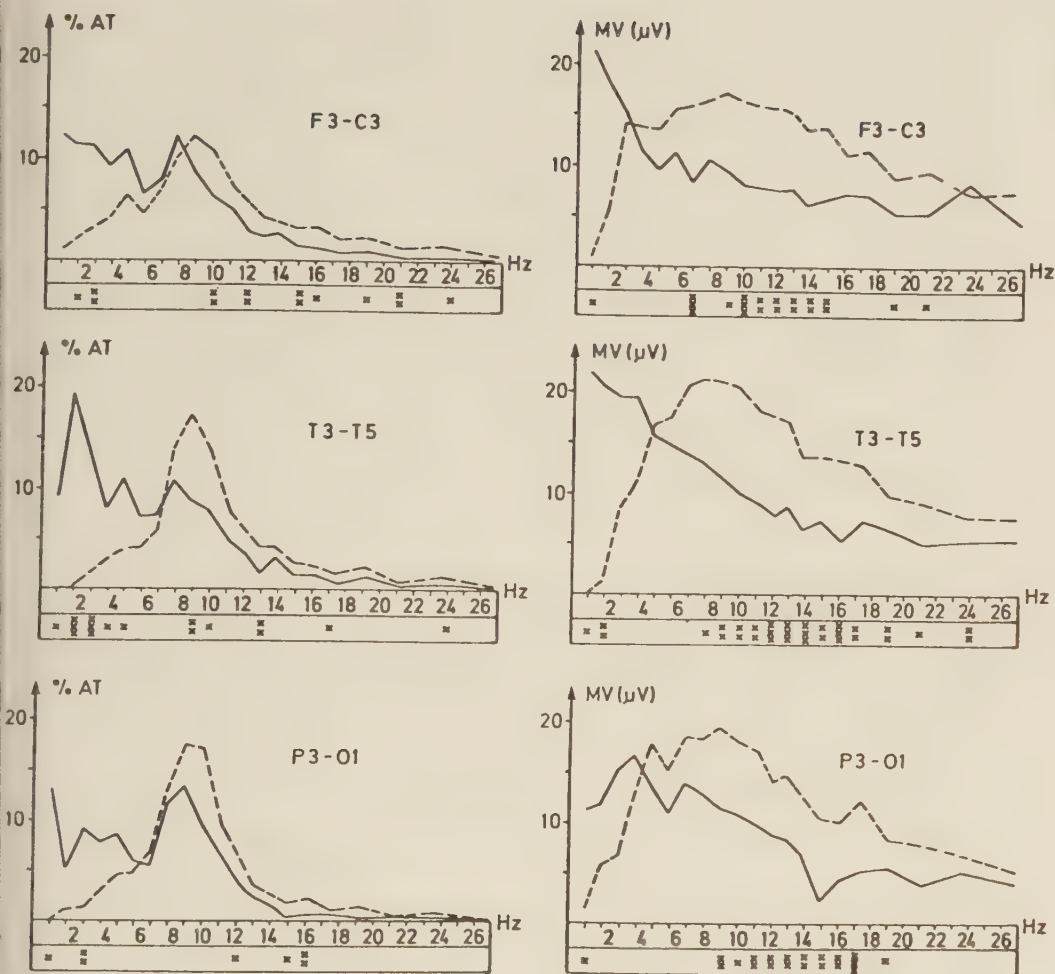


Fig. 2 b

the alpha activity was decreased as compared to the controls (Fig. 2 b). On visual evaluation, one of the four EEG's was found to be slightly to moderately abnormal due to a periodic general slowing of the background frequency, whereas the three others were considered to be normal. Even when only the three visually normal records were analysed quantitatively, the abnormal frequency pattern described above was confirmed. The mean "pre/post" frequency ratio was 0.96 (S.D.=0.17) which was not significantly different from that of the controls.

Pick versus Alzheimer

The MF in the Alzheimer patients was significantly lower than in the Pick patients (Table I). This was mainly due to more delta and theta activity in the Alzheimer group, and more alpha activity in the Pick patients. There was no difference in EEG mean voltage between the two groups. The mean "pre/post" frequency ratio of the Alzheimer patients was significantly higher ($p < 0.05$) than that of the Pick patients.

EEG related to regional cerebral blood flow

In a regional comparison the MF of the Pick patients correlated significantly with the f_g and f_w (Table IIa). Such a correlation was not found in the Alzheimer patients (Table IIb). Taking all patients together, a significant correlation was, however, only found between the MF and the f_w (Table IIc). The association

Table II a-c. Spearman Rank Correlation Coefficients indicating the relationship between EEG and rCBF parameters in the fronto-central, the temporal and the parieto-occipital regions of the left hemisphere of (a) the 4 patients with Pick's disease (number of observations=12), (b) the 6 patients with Alzheimer's disease (number of observations=18) and (c) the Pick and Alzheimer patients taken together (number of observations=30). The percentage activity time (%AT) accumulated in delta, theta, alpha and beta frequency bands, the EEG mean frequency (MF) and the EEG mean voltage (MVA) were compared to the mean cerebral blood flow (f_m), the grey matter flow (f_g), the white matter flow (f_w), and to the relative weight of the grey matter (w_g).

Table II a

rCBF parameters	E E G p a r a m e t e r s					
	MF	MVA	Delta %AT	Theta % AT	Alpha %AT	Beta %AT
f_m	.60*	-.62*	-.24	-.25	-.35	.49*
f_g	.67**	-.65*	-.19	-.55*	-.22	.48
f_w	.64*	-.59*	-.12	-.53*	-.18	.48
w_g	.17	-.54*	-.01	.09	-.48	.41

* p < 0.05

** p < 0.01

cont.

Table II b

rCBF parameters	E E G p a r a m e t e r s				
	MF	MVA	Delta %AT	Theta %AT	Alpha %AT Beta %AT
f _m	.05	-.03	.11	-.34	.02 .25
f _g	-.27	-.14	.38	-.35	-.21 -.14
f _w	.28	-.09	-.28	-.45*	.18 .24
w _g	.05	-.09	.05	-.24	-.03 .19

* p < 0.05

Table II c

rCBF parameters	E E G p a r a m e t e r s				
	MF	MVA	Delta %AT	Theta %AT	Alpha %AT Beta %AT
f _m	.27	-.23	-.11	-.36*	-.06 .32*
f _g	.09	-.35*	.04	-.38*	-.18 .09
f _w	.45**	-.26	-.33*	-.54**	.13 .30
w _g	.11	-.21	-.02	-.15	-.10 .23

* p < 0.05

** p < 0.01

between EEG frequency and blood flow was most prominent in the parieto-occipital region. Furthermore, the quantity of theta activity and the EEG mean voltage showed a significant negative correlation with the f_g and f_w , again most striking in the Pick patients (Table IIa-c).

The correlation between the "pre/post" EEG frequency ratio and the "pre/post" flow ratio taking all 10 patients together was highly significant, especially regarding the f_g (Table III).

Table III. The correlation coefficient (Spearman r_s) of the pre/postcentral EEG mean frequency (MF) ratio and the "pre/post" ratios of the mean cerebral blood flow (f_m), the grey matter blood flow (f_g), the white matter flow (f_w) and the relative weight^g of the grey matter (w_g) in all 10 patients.

"Pre/post" ratios				
EEG parameter	rCBF parameters			
	f_m	f_g	f_w	w_g
MF	.59*	.77***	.33	.53

* $p < 0.05$

*** $p < 0.001$

DISCUSSION

In this study the EEG and the regional cerebral blood flow has been investigated for the first time in a quantitative way in autopsy confirmed cases of Alzheimer's and Pick's disease. The number of patients were rather few, which expresses the difficulties to obtain material of this type. Two limiting factors in the study should be emphasized: first, the study was carried out entirely during resting conditions, and no activation procedures were applied. Second, the cerebral regions in which the rCBF was measured and the EEG recorded were only approximately the same.

In Pick's disease the quantitative EEG analysis showed that the EEG, even when visually interpreted as normal, was clearly different from that of a healthy control group. However, as expected from the visual analysis, the EEG abnormality of the Alzheimer patients was much more pronounced than in the Pick patients, a finding which is in accordance with previous studies (Letemendia and Pampiglione 1958, Swain 1959, Gordon and Sim 1967, Nevin 1967, Jóhannesson et al. 1977). The high pre/postcentral EEG frequency ratio of the Alzheimer patients also separated them from the Pick patients. This "hyperfrontality" of the EEG (Ingvar 1979, Ingvar et al. 1979) differed clearly from that seen in the controls. The abnormal, but different EEG pattern in Pick's and Alzheimer's disease are of differential diagnostic importance. They might be used in the diagnosis of organic dementia. Additionally an

early correct diagnosis is a prerequisite in treatment trials of Alzheimer's disease (Kendall 1979, Glen and Whalley 1979). Controlled quantitative EEG studies of other types of dementia, and of the reversible dementia-like diseases, are, however, needed before the usefulness of EEG in dementia diagnosis can finally be assessed.

The association between the EEG abnormality and the severity of the disease (Gordon and Sim 1967, Jöhanne-son et al. 1979) could not be further elucidated in the present study, because the patients were in almost equally advanced stage of the disease. Likewise, it was impossible to examine the relation between the duration of the disease and the degree of EEG abnormality, because the scatter of the duration was quite small.

The coupling between EEG frequency, cerebral blood flow and cerebral metabolic rate for oxygen is well established in animal experiments (Baldy-Moulinier and Ingvar 1968, Freeman and Ingvar 1968) and there is also substantial support for the existence of a similar coupling in man (Sulg 1969, Ingvar et al. 1976), even though there are certain important exceptions, e.g. in children and during sleep. A main question in this study was therefore, if EEG abnormalities expressed in quantitative values correlated with the regional cerebral blood flow in Alzheimer's and Pick's disease. Is it then possible, on the basis of EEG findings, to draw any conclusions about the rCBF in these disorders? For

the Pick patients this question could be answered positively, because of consistent significant correlations between EEG and rCBF parameters (Table IIa), whereas in the Alzheimer patients a distinct relationship between EEG and rCBF did not appear. However, the Alzheimer patients also contributed to the significant correlations found on taking all patients together. This was especially striking concerning the pre/postcentral ratio of rCBF and EEG, where the highest correlation between grey matter blood flow and EEG mean frequency was found (Table III). This implies that the interregional EEG relations reflect the interregional blood flow distribution in both types of dementia. The negative, although not statistically significant correlation between EEG frequency and the grey matter blood flow in the Alzheimer patients (Table IIb) was at variance with our primary assumption of a direct relationship between EEG frequency and rCBF. The precentral flow decrease in the Alzheimer patients was less pronounced and the postcentral flow decrease more pronounced than the EEG mean frequency indicated. However, this did not interfere with the highly significant correlation between pre/postcentral EEG frequency and rCBF ratios found in all patients, and was very much in agreement with the "hyperfrontal" flow distribution found in the Alzheimer patients, i.e. a high relative flow precentrally, and a low relative flow postcentrally, in spite of a reduced mean hemisphere blood flow (Ingvar et al. 1978). These CBF findings correlated with the predominant temporo-parieto-occipital cortical degeneration found in the Alzheimer patients (Brun and Gustafson 1976).

A possible explanation for the consistent correlations between EEG and rCBF in the Pick but not in the Alzheimer patients, could be a defective autoregulation in Alzheimer's disease, resulting in an uncoupling between rCBF and oxidative metabolism, the latter known to be closely associated with the EEG (Obrist et al. 1963, Ingvar et al. 1976). That an impaired autoregulation could be present in demented patients was indicated, but not proven, by the direct correlation between systemic blood pressure and cerebral blood flow recorded by Hedlund et al. (1964). However, in similar demented patients, Simard et al. (1971) found an intact autoregulation. A number of conditions are known to interrupt the cerebral autoregulation, e.g. hypoxia (Freeman and Ingvar 1968) in agreement with which there is no correlation between EEG and rCBF in cerebral infarction (Mosmans, thesis 1974, Kogure et al. 1980), acute hypertension (Strandgaard 1978), chronic alcoholism in some instances (Jóhannesson et al. 1980) and in experimental animals, increased "cerebral sensitivity to ammonia" along with portal systemic shunting (Gjedde et al. 1978). The existence of chronic cerebral hypoxia in Alzheimer's disease is, however, not likely. None of the other conditions mentioned were known to be present. The findings could, however, also be explained by a different pathology in the two diseases. Brain stem structures of importance for the regulation of the EEG activity are more often involved in Alzheimer's than in Pick's disease. The blood flow in the brain stem or the deeper brain structures was not measured by the present method. Therefore the influence

of EEG changes caused by brain stem dysfunction could not be taken into account. However, it should be mentioned that a diffuse rCBF reduction without corresponding gross loss of cortical neurones also could be found in severe brain stem lesions (Ingvar et al. 1964, Ingvar and Sourander 1970, Gustafson et al. 1977).

Another explanation for the dissociation between EEG and rCBF could be that of a different influence of the abnormal central cholinergic system in Alzheimer's disease (Davis and Maloney 1976, Perry et al. 1977, 1978, Smith and Swash 1978). The selective loss of cholinergic neurones (Bowen et al. 1977, 1979) could explain the reduction of CBF but hardly the EEG abnormalities, because as also pointed out by Roth (1979) "dead cells tell no tales". However, the reduced acetylcholine synthesis without concomitant changes in the overall glucose metabolism (Sims et al. 1980) could be the reason for the EEG abnormality, as anticholinergic drugs produce an EEG dominated by diffuse delta and theta activity without alteration of consciousness (Longo 1966). Direct correlation studies must be performed to establish the overall coupling between EEG frequency, blood flow and metabolism. This is now possible by means of positron emission tomography which measures regional cerebral metabolism non-invasively in man, not only in the cerebral cortex, but also in deep brain structures.

SUMMARY

The EEG in 9 Alzheimer and in 4 Pick patients, all confirmed at autopsy were studied. In all Pick patients, and in 6 of the 9 Alzheimer patients, the regional cerebral blood flow (rCBF) was measured in the left hemisphere, using the intra-arterial $^{133}\text{Xenon}$ clearance technique. Three EEG leads (F3-C3, T3-T5 and P3-O1) were analysed by means of a computer. The EEG's from 13 healthy volunteers matched for age served as controls.

The Alzheimer patients showed slowing of the EEG mean frequency in all regions, with increased delta and theta, and decreased alpha and beta. In contrast, the alpha was preserved parieto-occipitally in the Pick patients, who also showed delta and theta increase, although less so than the Alzheimer patients. The ratio between the mean frequency of the fronto-central and the parieto-occipital regions was increased in the Alzheimer and slightly, but insignificantly decreased in the Pick patients. The EEG in Pick's disease, which is usually considered to be relatively normal even in advanced stages of dementia, was thus clearly different from that of healthy controls.

In the Pick patients the regional EEG mean frequency correlated significantly to the corresponding regional flow values. This was not so in the Alzheimer patients indicating different pathophysiology in the two disorders. In all patients the EEG mean frequency correlated

significantly with the white matter blood flow. Also the quantity of theta activity and the EEG mean voltage showed a significant negative correlation with the regional grey and white matter blood flow, again most striking in the Pick patients.

ACKNOWLEDGEMENTS

The study was in part supported by a grant from "Else Thorps Legat till Fremme af Videnskabelig Forskning ved det Medicinske Fakultet". The computer work was performed at the Department of Data Processing in Medicine, Gentofte Hospital. Gudjón Jóhannesson and David H. Ingvar were aided by the Swedish Medical Research Council (project no. B80-14X00084-16B) and by the Wallenberg Foundation.

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EEG ABNORMALITIES IN CHRONIC ALCOHOLISM RELATED
TO AGE

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Acknowledgements: The study was supported by the
Swedish Medical Research Council (project no. B81-14X-
00084-17C and 21X-3950) and by the Wallenberg Founda-
tion in Stockholm

SUMMARY

The EEG was studied in 50 chronic alcoholics (age 45 ± 10 years). All EEGs were classified visually. Besides, a manual analysis from a fronto-central ($F_3 - C_3$ or $F_4 - C_4$) lead and a temporo-occipital ($T_5 - O_1$ or $T_6 - O_2$) lead was done in 42 cases to obtain the mean frequency of the 6-12 Hz band.

The visual classification correlated fairly well with the frequency analysis in the anterior ($r_s = -0.57$, $p < .001$) and in the posterior ($r_s = 0.61$, $p < .001$) leads and there was a high positive correlation between the frontal and occipital lead ($r = 0.88$, $p < .001$). Half of the records were abnormal. There was a significantly higher proportion of abnormal EEGs both in the youngest and oldest patient groups compared with the remainder. EEG-abnormality was significantly related to early start of abuse (before 25 years, $p < .05$). The findings might suggest that alcohol abuse in the teens or early twenties is accompanied by a considerably greater risk of brain damage than alcoholism beginning after 25. However, an alternative explanation, i.e. that the EEG abnormality may represent cerebral dysfunction predisposing to alcoholism is not excluded.

The percentage of abnormal EEG's in chronic alcoholism reported by different authors is variable, depending upon the type and severity of the disease in the particular studies, and also upon the varying criteria for EEG abnormality (Naitoh 1973, Begleiter & Platz 1972). In alcoholism without somatic complications or psychosis the occurrence of EEG abnormalities is relatively low (Funkhouser et al. 1953, Greenblatt 1944, Arentsen & Sindrup 1963, Dyken et al. 1961) whereas in alcoholics with such complications as delirium tremens and epileptic seizures, it is more frequent (Arentsen & Sindrup 1963).

Several authors have reported that the EEG abnormalities in alcoholics increase with age (Greenblatt 1944, Arentsen & Sindrup 1963, Newman 1978). Further, alcoholics with a normal EEG have less percent time alpha than healthy subjects (Davis et al. 1941, Funkhouser et al. 1953, Little & McAvoy 1952). The EEG changes are in many cases probably caused by the alcohol abuse. The possibility, that EEG abnormality may be an expression of brain dysfunction predisposing to alcoholism has, however, not been excluded.

In a previous study (Jóhannesson, Berglund & Ingvar 1980) we demonstrated that young as well as old alcoholics showed more EEG disturbances than middle-aged ones. In the present study we have analysed this finding further, and here we present a tentative explanation for it.

MATERIAL AND METHODS

Fifty-three male patients with chronic alcoholism but with no signs of Korsakoff's psychosis were studied. They were admitted to the Department of Psychiatry I at the University Hospital in Lund during the years of 1968-72. The mean age was 45 ± 10 (range 22-65 years). The general characteristics of the material, social and clinical features, have been described elsewhere (Berglund et al. 1977, Berglund & Ingvar 1976, Berglund, Leijonquist & Hörlén 1977, Berglund & Soneson 1976, Jóhannesson, Berglund & Ingvar 1980). The patients had a history of excessive alcohol abuse ranging from 5 to 40 years. The start of abuse was defined as the time when the first of the following symptoms of alcoholism was reported (Kaij 1960): (a) an abnormal craving for more alcohol after ingestion of small quantities, (b) regular occurrence of blackouts following ingestion, and (c) a physical dependence on alcohol indicated by withdrawal symptoms after drinking has been stopped. At least 2 symptoms had to be present for the diagnosis of chronic alcoholism to be made. None of the patients showed signs of delirium tremens (DT) at the time of the study while 14 reported previous episodes. No patient had an epileptic seizure during admission for the present study although 13 had had epileptic seizures during earlier abstinence periods. Two patients had hepatic cirrhosis and three others showed signs of hepatic dysfunction, but biopsies did not show cirrhosis.

All patients went through an extensive psychiatric and clinical examination including EEG and rCBF measurements with the intraarterial $^{133}\text{Xenon}$ clearance technique (Ingvar & Gustafson 1970, Sveinsdottir et al. 1971, Lassen & Ingvar 1972).

EEG recordings were performed in all cases after a mean of 16 ± 11 days of abstinences. If several records were available the record used in the present study was that obtained in closest time relation to the rCBF study. No patient had any remaining symptoms of withdrawal at that time. Most EEG's were recorded on a 16-channel Siemens-Elema EEG apparatus, the rest on an 8-channel Grass machine. The international 10-20 electrode placement system was used (Jasper 1958). The records were taken at rest, in wakefulness and conventional bipolar technique was used in all cases. In three cases the EEG had been discarded. Thus the remaining records from 50 patients could be used. They were evaluated visually and assigned to one of four classes according to the classification used in preceding reports (Jóhannesson et al. 1977, 1979, 1980). This classification is as follows:

1/ normal (N), 2/ slightly abnormal (P), 3/ moderately abnormal (PP), 4/ severely abnormal (PPP).

1/ The record was considered normal when it had a symmetrical alpha activity and contained only minimal quantities of slow waves. Further, records dominated by beta activity were classed as normal when there was no simultaneous increase of slow activity or asymmetry.

2/ Slightly abnormal records (P) contained an admixture of diffuse or episodic theta activity and/or slight slowing of the background (alpha) activity.

3/ Moderately abnormal records (PP) contained more theta and mostly some delta activity.

4/ Severely abnormal records (PPP) were mostly dominated by delta and theta activity, sometimes of an episodic nature.

Medication was kept as constant as possible during the week preceding the EEG examination. The evening before the EEG study usually 0.5 to 1.5 g of chloral hydrate was given if hypnotics were necessary (25 cases). The morning before the EEG study no drugs were given with the exception of premedication with 0.1 g phenobarbital and 0.5 mg atropin before the regional cerebral blood flow study if the two studies were done on the same day (in 18 cases).

All records were found to belong to one of the three first categories (N, P and PP). Samples of representative records for these classes are shown in Fig. 1. When the visual classification was compared with the results of the manual frequency analysis the classes were

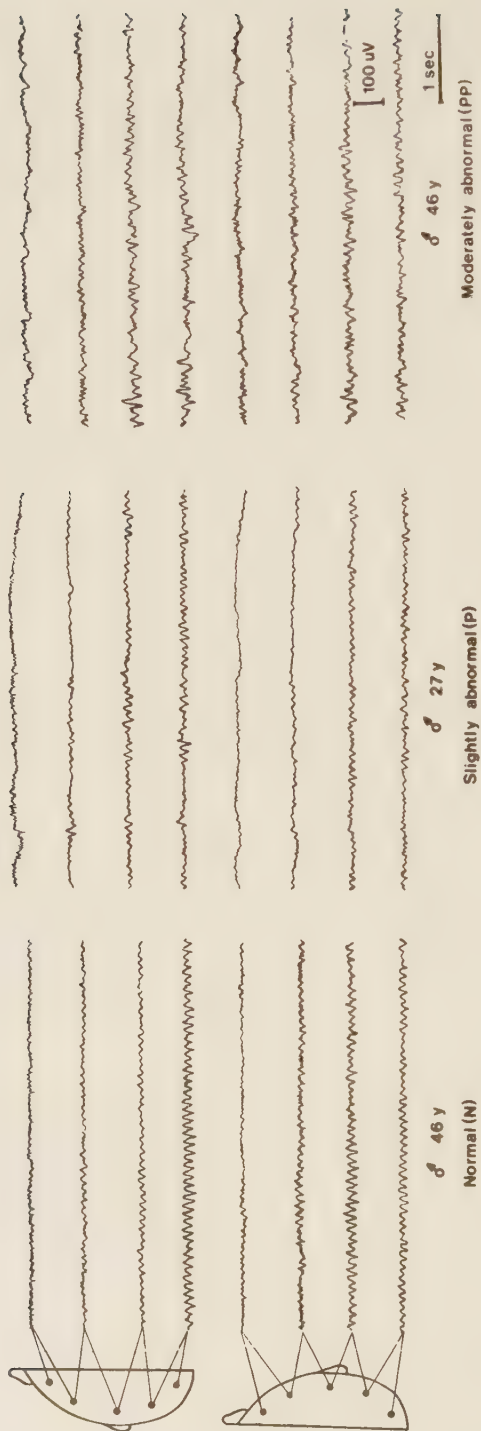


Figure 1 Representative samples of the visual EEG-classes. "N" (1) normal EEG, "p" (2) slightly abnormal EEG and "ppp" (3) moderately abnormal EEG.

simply treated thus: $N = 1$, $P = 2$, $PP = 3$. In one patient with a history of convulsions and delirium tremens the EEG contained questionable low voltage sharp waves, but distinct focal or paroxysmal abnormalities were not found in the present EEG material.

Increased beta activity was found in some records. In the present study this was, however, not quantified, and, as stated above, was not considered in the visual classification. Manual frequency analysis was done according to the method devised by Sulg (1969). This method is highly reliable, but time-consuming. The analysis was limited to the frequency bands 6-15 Hz. A ten seconds' epoch was analysed from representative samples of an anterior lead (fronto-central, FC) and a posterior lead (temporo-occipital, TO), respectively. The mean frequency was calculated for the 6-12 Hz band in each lead. Eight records were excluded from the analysis, either due to low voltage and/or presence of fast frequencies, or due to pronounced artefacts.

RESULTS

There was a high positive correlation between the mean frequency in anterior and in posterior leads ($r=0.88$, $p < .001$). A significant, but less strong negative correlation was found between the degree of abnormality on visual classification and the mean frequency in the anterior ($r_s=-0.57$, $p < .001$), and in the posterior ($r_s=-0.61$, $p < .001$, Spearman rank correlation coefficient) leads, respectively (Fig. 2). In the latter case a high correlation was not expected, since the manual analysis excluded the slowest waves (below 6 Hz), which on the other hand influenced the visual evaluation.

EEG and age

Half of the patients (25) had an abnormal EEG. The distribution of the EEG classes in different age groups is shown in Fig. 3. It is seen that the highest proportion of normal EEGs was found in the 40-49 years group. In older, as well as younger patients the greater part of the records were abnormal. In the younger group the abnormality was in most cases mild (P), whereas six out of eight of the moderately abnormal (PP) records were found in patients over 50 years. In the latter group, the abnormality clearly increased with age and all five patients 60 years or over had abnormal records. There was a statistically significant difference between the old (≥ 50 years) and the middle (40-49 years) groups ($\chi^2 = 6.61$, $p < .05$),

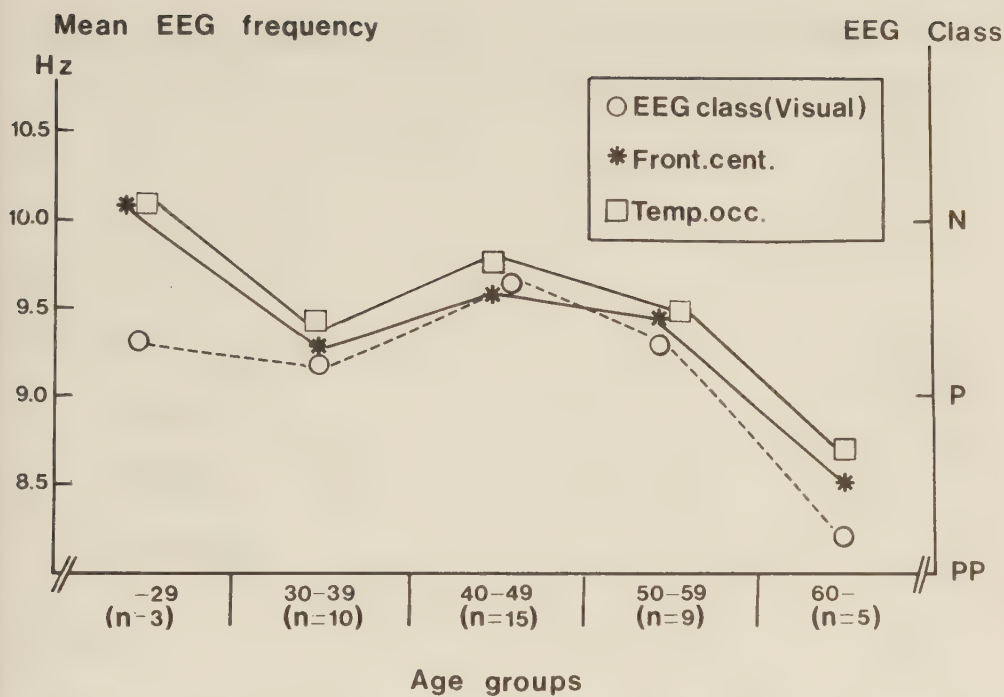


Figure 2 Comparison of visual EEG evaluation and mean EEG frequency in the fronto-central and temporo-occipital regions in different age groups. The visual classification was treated as a quantification with arbitrary units (N=1, P=2, PP=3). There was a good correlation between the fronto- central and temporo-occipital leads ($r=0.88$, $p < .001$) and a fairly good correlation also between the visual evaluation and the mean frequency in the fronto-central and temporo-occipital lead ($r_s=-0.57$, $p < .001$ and $r_s=-0.61$, $p < .001$, respectively, Spearman rank correlation).

and between the young (< 40 years) and the middle group ($\chi^2 = 7.73$, $p < .01$).

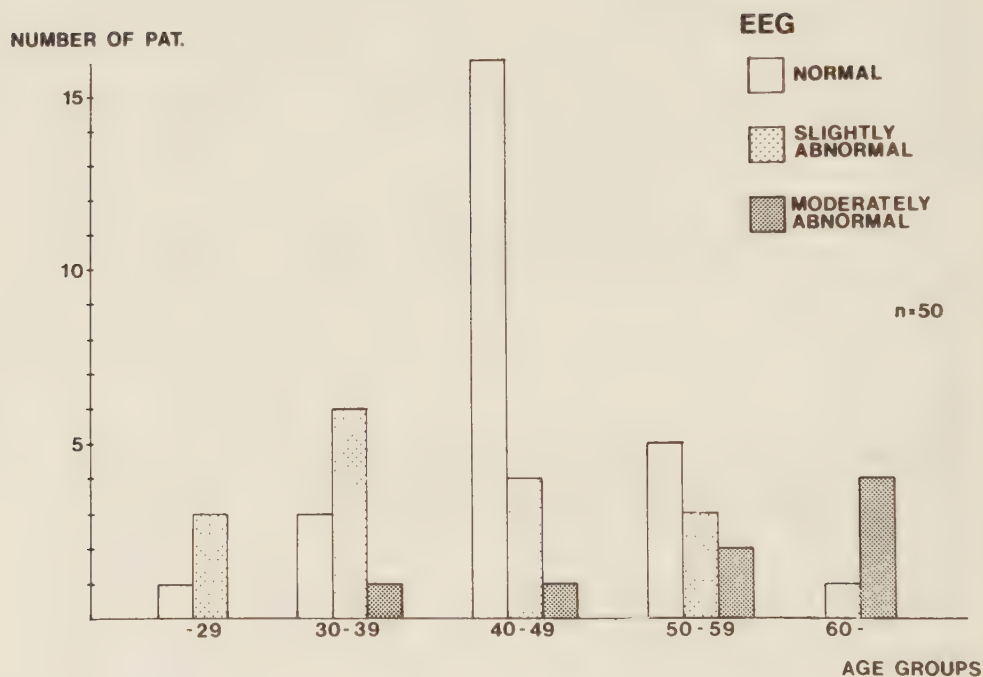


Figure 3 Visual classification of records in different age groups. The most abnormal EEGs are found in the oldest patients, whereas the majority of the young alcoholics (< 40 years) has a slightly abnormal EEG. For statistical significance, see text.

The temporo-occipital (TO) and the fronto-central (FC) mean frequency showed a negative correlation to age (TO and age: $r=-0.30$, n.s., FC and age: $r=-0.28$, n.s., $n = 42$). The correlation was higher in patients over 40 years (TO and age: $r=-0.42$, $p < .02$, FC and age: $r=-0.40$ $p < 0.05$, $n=29$).

EEG and clinical findings

The relation between EEG and age of onset of abuse is shown in Figs. 4 and 5.

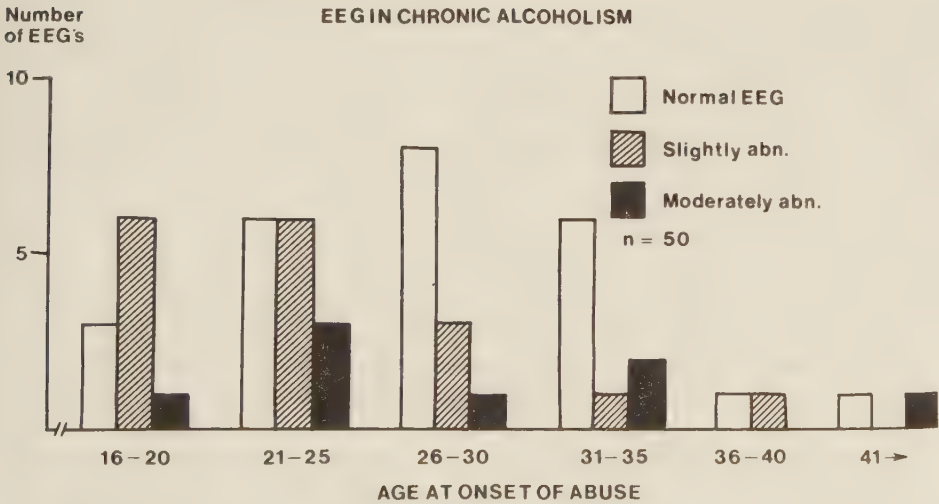


Figure 4 EEG classification related to age at onset of abuse. The proportion of abnormal EEGs was significantly greater in the group with early onset of abuse (up to 25) than in those with late onset (after 25 years). See text.

It is seen that the proportion of abnormal EEG's was greatest in those who had started drinking at the age of 16-20 years, and decreased with advancing age of onset (Fig. 5).

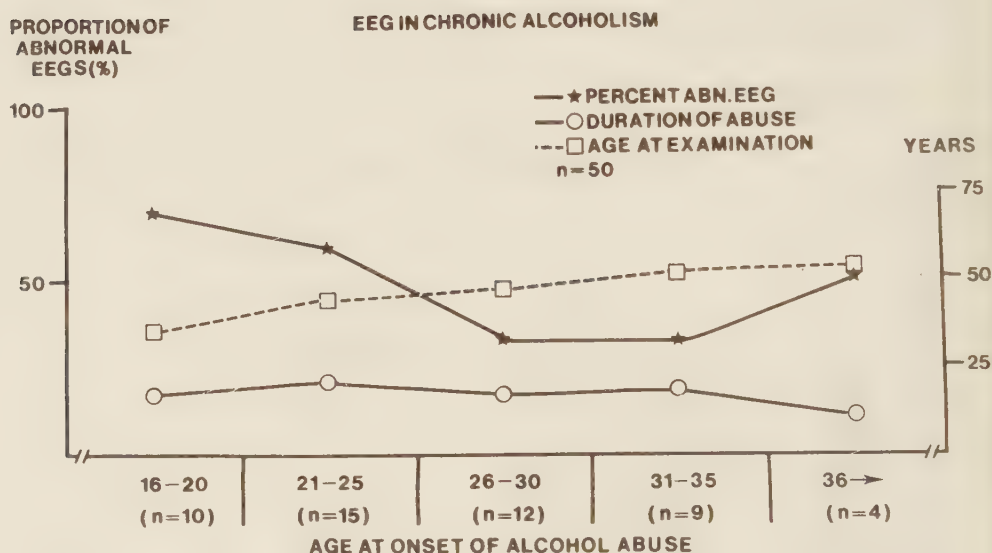


Figure 5 The relation of (1) the proportion of abnormal EEG, (2) duration of abuse, and (3) age at examination, to the age of onset of alcohol abuse.

The percentage of abnormal records decreased with advancing age of onset. The duration did not differ significantly between the early onset group and the late onset group and accordingly, the mean age at examination was the higher the later the abuse had begun.

The series was divided by a median cut into patients with early onset of abuse, i.e. up to 25 years of age, and those with a late onset, i.e. over 25 years. The mean duration of abuse was at the time of examination similar in the two groups (Fig. 5). In the group with early onset there were 16 patients with abnormal EEG whereas 9 had a normal EEG. In the late onset group (onset after 25 years) these numbers were reversed (16 normal, 9 abnormal). The difference is statistically significant ($\chi^2=3.92$, $p < .05$).

The group of patients with the longest duration of abuse (> 20 years) had a larger proportion of abnormal EEGs than the rest. The difference was not statistically significant. However, patients with moderately abnormal EEG ("PP") had a significantly longer duration of abuse than the others (25 ± 11 years against 17 ± 8 years, $p < .05$, Student's t-test).

Eight of the thirteen patients with a history of epileptic seizures during abstinence, ten out of fourteen patients with a history of delirium tremens, and 16 of the 28 patients with blackouts had an abnormal EEG with non-specific changes. The proportion of abnormal records in cases with these complications was, however, not significantly different from the remainder.

DISCUSSION

The two main findings in the present study are:

- a) A higher proportion of abnormal records in the youngest and oldest groups of alcoholics than in the age group in the middle.
- b) A correlation between early onset of abuse and abnormal EEG irrespective of the age at EEG examination.

The finding of more abnormal EEGs in the oldest alcoholics was expected, and confirms the results of earlier authors (Greenblatt 1944, Arentsen & Sindrup 1963, Newman 1978). Here the cause most reasonably is the cumulative damage caused by the alcohol abuse. This interpretation is supported by pathoanatomical studies (Courville 1955), by recent computer tomography studies (Wilkinson & Carlén 1980, Bergman et al. 1980) and also by regional cerebral blood flow studies (Berglund & Ingvar 1976). The underlying mechanisms are not well understood. The most probable cause is a direct effect of alcohol on the nerve cells leading to an acceleration of the normal aging (Courville 1955, Wilkinson & Carlén 1980).

Other possible mechanisms might be a clinically undiagnosed Wernicke-Korsakoff syndrome which in recent studies has been shown to be more common than previously assumed (Harper 1979), white matter degeneration (Lynch 1960, Berglund & Ingvar 1976), and hepatic dysfunction with secondary toxic effects on the brain.

However, as will be shown in a forthcoming study, evidence of liver dysfunction was not consistently associated with EEG abnormality (Jóhannesson, Berglund & Ingvar 1981).

The high proportion of abnormal EEGs in young alcoholics was, on the other hand, not expected. In the comprehensive and thorough study of Arentsen & Sindrup (1963), the proportion of abnormal EEGs was also high in the youngest patients, a finding later pointed out by Begleiter & Platz (1972). The similarities between the relative distribution of EEG abnormality in our material and that of Arentsen & Sindrup (1963) are interesting, since their case material included less severe alcoholics, and, consequently, the total proportion of abnormal records in their study was much lower.

Further analysis of our material showed that EEG-abnormality was significantly related to the age of onset of abuse. This has not been reported previously, as far - as we know. There are, at least, two possible explanations for this finding. First, the young, not fully matured brain may be more sensitive to alcohol than the adult brain. Second, the EEG abnormality might have been present prior to the onset of the abuse and thus represent brain pathology, genetically determined, or postnatally acquired. This pathology might thus have been the cause and not the effect of the alcoholism.

It would be reasonable to assume that the young (adolescent) brain is more sensitive than the adult brain to neurotoxic agents, such as alcohol. The maturation of the EEG, which most likely reflects the maturation of the neurons of the brain, is not completed until after the age of twenty (Eeg-Olofsson 1970). It is also known that the young brain has a higher oxidative metabolism than the old brain (Kennedy et al. 1957). This may also make the young brain more vulnerable to metabolic interference.

The second explanation is supported by some adoption studies as far as the genetic factors is concerned. It has been found that the genetic type of alcoholism starts early (Goodwin et al. 1973, Bohman 1978). There are also reports that hyperactive children with minimal brain dysfunction often develop alcoholism (Goodwin et al. 1975).

To sum up: The most important result of this study was that an early start of alcohol abuse was related to an increased frequency of EEG abnormality.

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REDUCTION OF BLOOD FLOW IN CEREBRAL WHITE MATTER
IN ALCOHOLICS RELATED TO HEPATIC FUNCTION
A CBF and EEG study

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Acknowledgements: The study was supported by the
Swedish Medical Research Council (project no. B81-14X-
00084-17C and 21X-3950) and by the Wallenberg Founda-
tion in Stockholm

SUMMARY

Fifty alcoholics with a mean age of 45 years were examined with the intra-arterial ^{133}Xe method for measurement of regional cerebral blood flow and with EEG. The results were related to liver function tests. Reduced white matter blood flow correlated strongly with abnormal liver function tests. The highest correlation was with S-ASAT. Only weak correlations were found between gray matter flow, EEG and the liver function tests. It is suggested that the relationship between white matter flow reduction and liver function may be caused by the intensity of drinking prior to admission and possibly mediated by some still unknown hepatic mechanism or a direct effect of alcohol.

Hepatic insufficiency in cirrhosis is one of the causes of EEG abnormalities in alcoholism. These EEG changes, which are not specific for alcoholics, are well-known (Silverman 1962) and the degree of EEG slowing has been shown to correlate with the degree of liver dysfunction (Kardel et al. 1972, Kardel & Stigsby 1975). Abnormal EEG is also frequently found in alcoholics with delirium tremens and convulsions, even without signs of hepatic cirrhosis (Arentsen & Sindrup 1963, Begleiter & Platz 1972). However, cirrhosis of the liver and complications like delirium tremens and convulsions cannot readily explain all cases of abnormal EEG reported in the literature (Begleiter & Platz 1972).

In the present study we have analysed the relationship of cerebral function and hepatic disturbances of less severity than the liver insufficiency found in cirrhosis. Cerebral function was studied with measurements of the regional cerebral blood flow (rCBF) as well as with EEG.

The rCBF measurements yield isotope clearance curves from several brain regions simultaneously. Biexponential analysis of such clearance curves, obtained after injection of $^{133}\text{Xenon}$, yields separate estimates of a fast component, representing mainly the blood flow in the gray matter, and a slow component, representing mainly the blood flow of the white matter (Ingvar & Gustafson 1970, Sveinsdottir et al. 1971, Lassen & Ingvar 1972).

The blood flow in the cerebral white matter (f_w) has been far less studied than that of the gray matter (f_g), and/or the "total" flow (the mean flow in gray and white matter, here labelled F10).

The separate study of the f_g and f_w may, however, be crucial for the understanding of the mechanism behind the development of cerebral dysfunction in alcoholism.

Ingvar et al. (1969) and Berglund & Ingvar (1976), using the intraarterial $^{133}\text{Xenon}$ method, found a decrease of f_g , as well as of f_w , in alcoholism. Further, they observed that the f_g correlated significantly with age, while the f_w did not.

We have previously reported that there is an association in alcoholism between liver function and rCBF, as well as EEG, even in the absence of clinical signs of hepatic insufficiency (Jóhannesson et al. 1980). In the present paper we have analysed further the relationship between hepatic function and (1) the cerebral blood flow in the two main cerebral tissue compartments, the gray, and the white matter, and (2) the EEG.

MATERIAL AND METHODS

The material consists of fifty male patients (after excluding 3 cases in which EEG was not available) with chronic alcoholism, without signs of Korsakoff's psychosis who were admitted to the Department of Psychiatry at the University Hospital in Lund during the years 1968-72. The mean age was 45 ± 10 (range 22-65 years). The general characteristics of the material, social and clinical features, have been described elsewhere (Berglund et al. 1977a, b, Berglund & Ingvar 1976, Berglund & Sonesson 1976, Jóhannesson, Berglund & Ingvar 1981). All patients had a history of excessive alcohol abuse ranging from 5 to 40 years. Three patients had a moderate arterial hypertension (over 170 mm Hg systolic or 100 mm Hg diastolic). One of them had a moderately enlarged heart and retinopathy. One patient showed some respiratory insufficiency and another had a mild diabetes without complications. One patient had been hospitalized for a brain contusion at the age of 4 years without neurological sequelae. The onset of abuse was defined as the time when the first of the following symptoms of alcoholism was reported (Kaij 1960): (a) an abnormal craving for more alcohol after ingestion of small quantities, (b) regular occurrence of blackouts following ingestion of alcohol, and (c) physical dependence on alcohol indicated by withdrawal symptoms when drinking has been stopped. At least two of these symptoms had to be present for the diagnosis of chronic alcoholism to be made. No patient showed signs of delirium tremens (DT) at the time of

the study while 14 reported previous DT episodes. No patient had epileptic seizures at admission or during hospital stay for the present study but 13 had had epileptic seizures during earlier abstinence periods. Two patients had hepatic cirrhosis and three others showed signs of hepatic dysfunction, although biopsy did not show cirrhosis. No patient had clinical signs of hepatic encephalopathy.

The psychiatric and clinical examination included EEG and measurement of the regional cerebral blood flow (rCBF) with the intraarterial ^{133}Xe clearance technique (Ingvar & Gustafson 1970, Sveinsdottir et al. 1971, Lassen & Ingvar 1972). The rCBF study was done in the dominant hemisphere in all but 8 cases. The measurements were generally made more than one week after admission (mean 16 ± 11 days: range 2-46). In no case were there any remaining withdrawal symptoms at the time of the CBF study. In the first part of the study eight detectors were used, but then in about half of the cases a 32-detector apparatus was used. In order that all cases could be compared, the latter were converted to 8 regions by averaging the values from the area approximately corresponding to each of the eight detector regions of the older apparatus. The approximate localisation of the detectors is shown in fig. 1. Regional values for the four rCBF parameters were obtained as follows: Mean flow (f_{10}) was calculated according to the height-over-area principle from the first 10 minutes of the clearance curve, f_g was calculated from the fast component obtained by biexponential

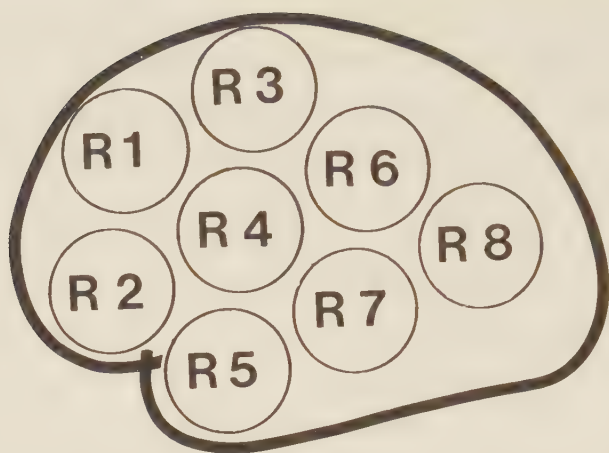


Figure 1 Approximate localization of detector regions in which rCBF was measured: R1/ Upper frontal, R2/ Lower frontal, R3/ Premotor, R4/ Motor, R5/ Anterior temporal, R6/ Parietal, R7/ Posterior temporal, R8/ Occipital.

analysis of the clearance curve, representing mainly the flow in the gray matter, and f_w from the slow component yielded by the biexponential analysis of the clearance curve, representing mainly the blood flow in white matter: and $g\%$, the relative weight of the gray matter, calculated from the biexponential analysis of the clearance curve from the intercepts at time zero for the fast and slow components. Blood samples for determination of $paCO_2$ were taken in connection with the blood flow measurements. The general results of the rCBF study and its correlations with clinical variables have been reported previously (Berglund & Ingvar 1976).

EEG studies were done in all cases, in most cases several recordings. One record was taken in close time relation to the rCBF measurement, and that record was

used in this study. In most cases a Siemens-Elema EEG machine was used, in some a Grass apparatus. Recording was done at rest in wakefulness with closed eyes. Electrode placement was according to the 10-20 international system (Jasper 1958). The EEG records were evaluated visually and assigned to one of four classes according to the classification used in preceding reports (Jóhannesson et al. 1977, 1979, 1981) as follows: 1/ normal (N), 2/ slightly abnormal (P), 3/ moderately abnormal (PP), 4/ severely abnormal (PPP). The criteria are described elsewhere (Jóhannesson 1981). Class 4 (PPP) severely abnormal, did not occur in the present series of EEG records.

Manual analysis was done according to the method devised by Sulg (1969). An analysis limited to the frequency classes 6 to 15 Hz was done in an anterior (fronto-central FC) and a posterior (temporo-occipital TO) lead and the mean frequency was calculated for the frequency band 6-12 Hz in each lead. Further, the ratio between the mean frequency in the anterior and the posterior lead was calculated as $A/P = \frac{FC}{TO}$.

Laboratory studies on admission included aspartate aminotransferase (S-ASAT, GOT), alanine aminotransferase (S-ALAT, GPT) and S-bilirubin. Bromsulphthalein retention test (BSP) was done on the day before or after the rCBF study. Liver biopsy was done in 19 cases, most of whom had abnormal BSP.

Medication was kept as constant as possible during the examination days. The evening before the rCBF study usually 0.5 to 1.5 g of chloral hydrate was given if hypnotics were necessary.

Statistical methods: Product moment correlation was used only to calculate the partial correlations in table 4 and the correlation between paCO_2 and flow values. Because of the non-Gaussian distribution of the liver test values Spearman rank correlation (Siegel 1956) was used in all other cases.

RESULTS

Liver tests

Table 1 shows the results of the liver tests and the normal values. The majority of the patients or 29 had bromsulphthalein retention (BSP) values within normal limits ($\leq 7\%$ up to 35 years, thereafter $0.2 \times$ age in years). In 17 cases it was abnormal. In 24 patients S-ASAT was within normal limits (< 0.67 uKat/l) but increased in 23 cases. S-ALAT was normal (< 0.67 uKat/l) in 28 cases, increased in 19 patients. Total bilirubin was normal ($3-20$ umol/l) in 35 and increased in 11 cases. In table 2 the intercorrelations between the four liver tests are seen. There was a high correlation ($r_s=0.80$, $p < .001$) between the two transaminases and in all other cases the correlations between each two tests were significant, even if the correlations of ALAT with BSP and bilirubin were low.

The blood flow in the gray matter as well as in the white matter was significantly reduced compared to healthy controls. On the other hand, the relative weight of the gray matter (g %) was not reduced. The general findings of the blood flow study have been reported previously (Berglund and Ingvar 1976). The EEG was abnormal in half of the cases: in 8 of these the abnormality was moderate (PP), in 17 it was mild (P). The details of the EEG findings are described elsewhere (Jóhannesson et al. 1981).

Table 1. Results of liver tests

	Normal	Abnormal	Total	Normal range
BSP	29	17	46	up to 35 yrs: $\leq 7\%$ after 35 yrs: $0.2 \times \text{age}$
S-ASAT	24	23	47	$\leq 0.67 \mu\text{kat/l}$
S-ALAT	28	19	47	$\leq 0.67 \mu\text{kat/l}$
S-BIL	35	11	46	$3 - 20 \mu\text{mol/l}$

Table 2. Intercorrelations between the liver tests: bromsulphthalein retention (BSP). S-ASAT (GOT), S-ALAT (GPT) and bilirubin. Spearman rank correlation coefficient (rs).

	BSP	S-ASAT	S-ALAT	BIL
BSP	X	.38**	.31*	.51***
S-ASAT	.38**	X	.80***	.38**
S-ALAT	.31*	.80***	X	.29*
BIL	.51***	.38**	.29*	X

* $p < .05$

** $p < .01$

*** $p < .001$

Correlations with age variables

Table 3 shows the correlation of the bromsulphthalein retention test (BSP), the transaminases (ASAT and ALAT) and bilirubin with the age at examination, age at onset of abuse and duration of abuse (Spearman rank correlation coefficient). BSP showed a significant positive correlation with age ($p < .05$) and duration of alcohol abuse ($p < .01$), while there was no correlation at all with the age at onset of abuse. The transaminases showed the same tendency, which, however, was significant only between ASAT and duration of abuse ($p < .05$). The serum bilirubin had no correlation with the age variables.

Table 3. Correlation of BSP, S-ASAT, S-ALAT and serum bilirubin with age at examination, age at onset of abuse and duration of abuse (years).
Spearman rank correlation coefficient (rs).

	BSP	S-ASAT	S-ALAT	BIL
Age at examination	.27*	.18	.16	.04
Age at onset of abuse	-.00	-.03	.04	-.00
Duration of abuse	.35**	.32*	.19	.04

* $p < .05$

** $p < .01$

EEG

In table 4 the correlations of the four EEG variables with the liver values are shown. There was no significant correlation between the liver tests and the degree of EEG abnormality or the frontocentral mean frequency (FC). On the other hand there was significant positive correlation between BSP and the temporo-occipital mean frequency (TO). This finding has not been further analysed. All the liver variables were negatively correlated to the EEG A/P ratio, although only S-ASAT was significantly so.

Table 4. Spearman rank correlation coefficients (rs) of BSP, S-ASAT, S-ALAT and serum bilirubin with the four EEG variables: EEG abnormality, frontocentral mean frequency (FC), temporo-occipital mean frequency (TO) and the EEG A/P ratio.

	BSP	S-ASAT	S-ALAT	BIL
EEG abnormality	-.04	.05	.05	.05
FC frequency	.11	-.08	-.03	-.11
TO frequency	.28*	.15	.09	.04
EEG-A/P ratio	-.24	-.29*	-.16	-.25

* $p < .05$

Cerebral blood flow and liver function

The Spearman rank correlations of the rCBF mean hemispheric values with age at examination, age at onset of abuse and duration of abuse are presented in table 5. As expected, the gray matter flow (f_g) and the total flow (f_{10}), as well as the relative weight of the gray matter (g %) showed a significant negative correlation to age. By contrast there was no significant correlation at all between the white matter flow (f_w) and age at examination, onset of abuse, or duration of abuse.

Table 5. Correlations of age at examination, age at onset of abuse and duration of abuse with rCBF mean hemispheric values.

Spearman rank correlation coefficient, rs.

	F10	FG	FW	G %
Age at examination	-.46***	-.44**	-.04	-.45**
Age at onset of abuse	-.33*	-.32*	.14	-.27*
Duration of abuse	-.23	-.17	-.09	-.37**

* p < .05

** p < .01

*** p < .001

The age at onset of abuse showed a significant negative correlation with f_{10} ($p < .05$), the gray matter flow ($p < .05$), and the g % ($p < .05$). g % was the only CBF variable that correlated significantly with duration ($r_s = -0.37$, $p < .01$). In order to check a possible influence of $paCO_2$ on the results, correlations between $paCO_2$ and f_g and f_w respectively were calculated. No such association was found ($r = .08$ and $r = .07$ respectively).

Partial correlations were calculated for BSP and the flow variables. They are presented in fig. 2 to show the different effect on the correlation of BSP to the gray matter flow and the white matter flow respectively, when age was partialled out. As this illustrates strikingly the different nature of the f_g and f_w , we present it here, since an adequate non-parametric method was not available. The BSP values are not normally distributed which is to be borne in mind.

As can be seen (fig. 2) when age is partialled out, all except two regional correlations between f_g and BSP turn insignificant. By contrast the correlations between f_w and BSP remained unchanged or increase slightly.

RELATIONSHIP OF BSP TO GREY AND WHITE MATTER BLOOD FLOW PARTIAL CORRELATIONS

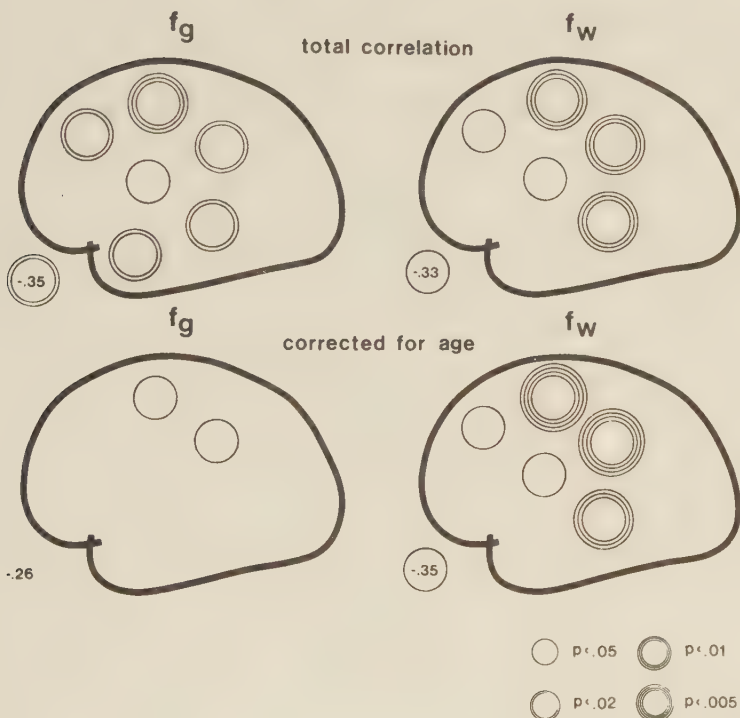


Figure 2 Partial correlations of BSP with f_g and f_w . The significance levels of the regional and mean hemispheric correlations are denoted by circles. One circle: $p < .05$, two circles: $p < .02$, three circles: $p < .01$, four circles: $p < .005$. When age is partialled out the correlation of BSP with hemispheric mean f_g becomes non-significant, and all regional correlations f_g decrease, only two of them remaining significant. On the other hand, correlations of BSP to f_w are unchanged or even slightly increased, when age f_w is partialled out. The numbers in front of each figure are correlations with the mean hemispheric flow values.

Fig. 3 shows the Spearman rank correlation coefficients (rs) between the liver variables and the regional and mean flow values of f_g and f_w . Here the effect of age inevitably is included. The correlations to BSP are generally weaker, as well for f_w as for f_g , but the regional pattern is similar to that of fig. 2 (total correlation). On the other hand there are distinct correlations between ASAT and ALAT and the white matter mean flow ($p < .02$ and $p < .05$ respectively). ASAT is highly correlated to the f_w regional values in the upper detector regions of the convexity and in the occipital region ($p < .005$ in the regions labelled R3 and R6 in fig. 1). The correlations of ALAT with the f_w regional values followed the same pattern as those of ASAT, although they were weaker. The transaminases showed low negative correlations with all regional f_g values, and with one exception, they did not reach statistical significance. Bilirubin correlated negatively with f_w regional values, showing almost the same pattern as the transaminases. The correlation to the mean hemispheric f_w value was not significant. The correlations of bilirubin with the gray matter flow were similar to those with the f_w , but showed fewer significances. It may finally be noted that in the anterior temporal region (R5) correlations to liver test values were absent. The same was true of the adjacent lower frontal region (R2) for BSP and bilirubin.

f_g AND f_w VERSUS LIVER FUNCTION

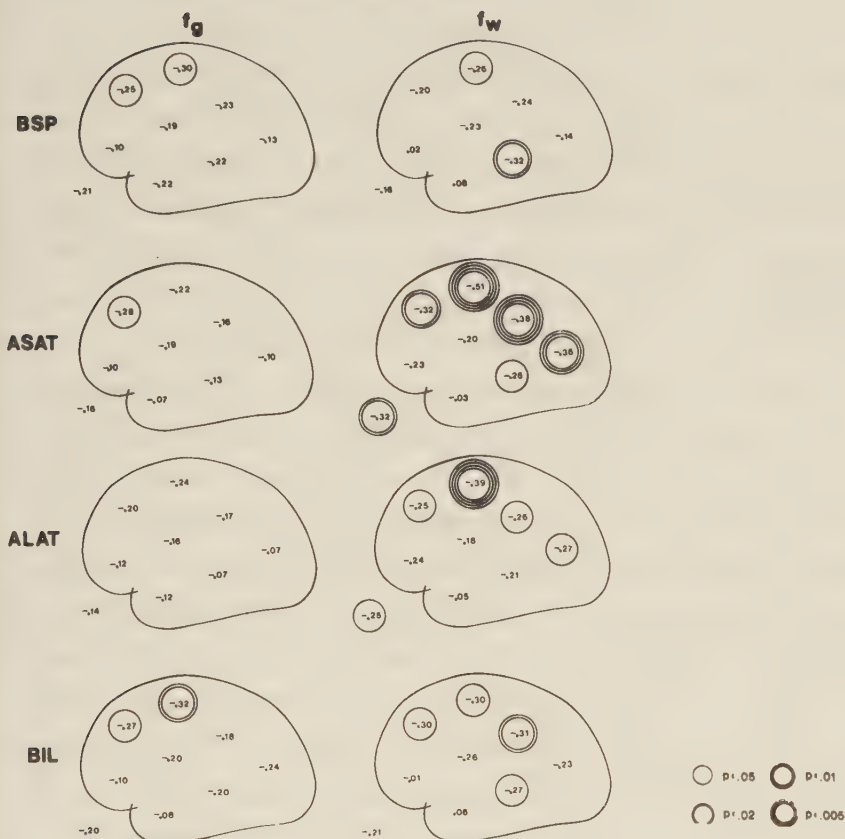


Figure 3 Relation of liver tests to f_g and f_w . The regional correlations are shown by Spearman rank correlation coefficients (r_s) in the detector locations and the correlations with hemispheric means in the same way in front of each figure. Significance levels are denoted in the same way as in fig. 2. Note that no correction is made for age.

The correlations of liver tests with f_g are low, the correlations with hemispheric means being non-significant and few regional values are statistically significant. On the other hand, there is a significant negative correlation between the transaminase values and the f_w mean and a highly significant correlation between S-ASAT and the f_w values in the upper regions of the convexity, and in the occipital region.

DISCUSSION

The main positive finding of the present study was a relationship between reduction of the blood flow in the cerebral white matter (f_w) and abnormal liver function tests and has, as far as we know, not been reported previously. Neither cerebral gray matter flow (f_g) nor EEG showed a similar relationship to liver function tests. Our results indicate that the reduction of f_g and f_w respectively may be caused by different mechanisms. In a previous report from this series of alcoholics (Berglund & Ingvar 1976) it was found that, with advancing age, the f_g decreased, and the reduction was most pronounced in patients older than 50 years. This finding, which is paralleled by the results of some neuroradiological studies (e.g. Wilkinson et al. 1980, Bergman et al. 1980), probably indicates loss of nerve cells and may possibly be caused by a combination of prolonged alcohol abuse and aging (Wilkinson et al. 1980).

The age-independent reduction of f_w is probably caused by other factors. One possible explanation is that the f_w reduction reflects demyelination or, perhaps, a stage preceding demyelination in the brain. Disturbances of the cerebral white matter in alcoholism have not been much studied with the exception of pontine myelinolysis and primary degeneration of the corpus callosum (Marchiafava-Bignami's disease, see review by Wright 1979). However, Lynch (1960) has described white matter changes in "ordinary" alcoholics. Further, in

brains from subjects with alcoholic liver disease, Lesch et al. (1972) found a significant loss of structural lipids in myelin rich areas. Alling & Boström (1980) also described loss of myelinated fibres and decreased concentration of cerebrosides, cholesterol and phospholipids in the mamillary bodies of brains from alcoholics. Finally, Sun (1980) has reviewed the literature on myelin changes in animal studies. The available evidence thus lends support to the idea that the present findings may reflect a specific damage to the white matter caused by alcohol.

Unexpectedly the regional f_w was better correlated to the transaminase values obtained at admission than to the BSP test that was done on the day before or after the rCBF study, on the average about two weeks after admission.

The association between the transaminase increases at admission and the drinking pattern immediately before admission is still poorly understood. Bang et al. (1958) found a significant relationship between S-ASAT activity and the blood alcohol concentration (BAC) probably indicating the severity of the abuse. However, Wadstein & Skude (1979) could not confirm this finding. One possible explanation of the present results might thus be that the f_w reduction is dependent on the intensity of the preceding alcohol consumption. In the present study we cannot conclude if the f_w reduction is reversible or not.

Preliminary observations (Johannesson et al. 1980) indicate that the liver disturbance in alcoholism may affect the relationship between EEG and rCBF, and that there may be an "uncoupling" of the normal close relationship between function and flow in the central nervous system. (See Ingvar and Lassen, 1975, and Gjedde et al. 1978).

The EEG-variables showed no simple relationship to the cerebral blood flow. The negative correlation between the liver test values and the EEG-A/P ratio might indicate that when the liver function is disturbed, the normal "hyperfrontality" of the EEG (Ingvar et al. 1979) is lost or reversed.

In contrast of the findings of Kardel and Stigsby (1975) who in patients with cirrhosis of the liver found an age-independent significant positive correlation between galactose elimination capacity and the dominant EEG frequency, we found no simple relationship between EEG and the hepatic test values. There is, however, a large difference between the present group of patients, most of whom had no clinical signs of hepatic insufficiency, and the cirrhotic patients of Kardel and Stigsby (1975).

Further analysis of the EEG-findings will be dealt with in a separate report (Johannesson, Berglund & Ingvar, 1981, to be published).

The flow reduction in the cerebral gray and white matter respectively apparently is of a different nature, the f_g being dependent upon age, and only weakly correlated to the transaminase values, while the reverse seems to be true of the f_w . This indicates a difference in the reaction of f_g and f_w to hepatic insufficiency, or some other pathological factors found in alcoholism.

Several studies on CBF indicate that f_g and f_w may react differently to paCO_2 changes (Olesen 1974) and arterial hypertension (Strandgaard 1978). The studies generally indicate that f_w is less sensitive than f_g to the above mentioned condition. There is evidence of a difference in the regulation of f_g and f_w , but at present the nature of this difference is unknown.

The mechanism by which alcohol exerts its effect on the blood flow of the cerebral white matter is unknown. It may be a toxic effect on nerve fibres, or an indirect effect via e.g. some toxic liver factor.

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